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SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

SERIAL RECORD AUG 1

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CONTENTS

Original Communications

Total Gastrectomy; Effects Upon Nutrition and Hematopoiesis. J. Matthews Farris, M.D., Henry K. Ransom, M.D., and Frederick A. Coller, M.D., Ann Arbor, Mich. ---- 823

Intestinal Strangulating Obstruction With Negative Roentgenologic Findings. Leon Goldman, M.D., San Francisco, Calif. ---- 834

Experimental Studies of the Value of Sulfathiazole in Peritonitis. Edgar J. Poth, M.D., Ph.D., Galveston, Texas, and E. Bravo Fernandez, M.D., Baltimore, Md. ---- 847

Anoxia and Anesthesia in Intrathoracic Operations. W. E. Adams, M.D., T. F. Thornton, Jr., M.D. (by invitation), A. J. Carlson, M.D. (by invitation), and H. M. Livingstone, M.D. (by invitation), Chicago, Ill. ---- 859

Silver Plug as a Method of Bronchial Closure in Experimental Pneumonectomy. Sol Roy Rosenthal, M.D. (by invitation), Willard Van Hazel, M.D. (by invitation), and Carl Ireneus, Jr., M.D., Chicago, Ill. ---- 880

The Protein and Fluid Balance in Experimental Shock Produced by Intestinal Trauma. Joe W. Howland, M.D., Earle B. Mahoney, M.D., Rochester, N. Y. ---- 889

Prolonged Dependent Drainage With "Lucite" Drains in the Treatment of Chronic Osteomyelitis. Clarence Dennis, M.D., Minneapolis, Minn. ---- 900

Radical Operation for Intractable Pruritus Ani. Forrest Young, M.D., and W. J. M. Scott, M.D., Rochester, N. Y. ---- 911

Gastric Acidity Following Gastric Resection. Cranston W. Holman, M.D., and Barton McSwain, M.D., New York, N. Y. ---- 916

Acute Abdominal Symptoms in Arachnidism. Harwell Wilson, M.D., Memphis, Tenn. ---- 924

An Evaluation of Some of the Materials Commonly Used for the Preoperative Preparation of the Skin. C. Alexander Hatfield, M.D., and John S. Lockwood, M.D., Philadelphia, Pa. 931

Resection of the Colon in Six Cases of Hirschsprung's Disease. Louise Yeazell, M.D., and H. Glenn Bell, M.D., San Francisco, Calif. ---- 941

Postcholecystectomy Rupture of the Common Bile Duct. Alexander Brunschwig, M.D., Chicago, Ill. ---- 951

Management of the Appendical Stump. John V. Goode, M.D., and Louis A. Kregel, M.D., Dallas, Texas ---- 956

Recent Advances in Surgery

Studies of the Circulation in Clinical Shock. A. Cournand, M.D., R. L. Riley, M.D., S. E. Bradley, M.D., E. S. Breed, M.D., R. P. Noble, M.D., H. D. Lauson, M.D., M. I. Gregersen, Ph.D., and D. W. Richards, M.D., New York, N. Y. ---- 964

Review of Recent Meetings

Review of Fifth Annual Meeting of the Society of University Surgeons. Alexander Brunschwig, M.D., Chicago, Ill. ---- 996

Index

Index ---- 997

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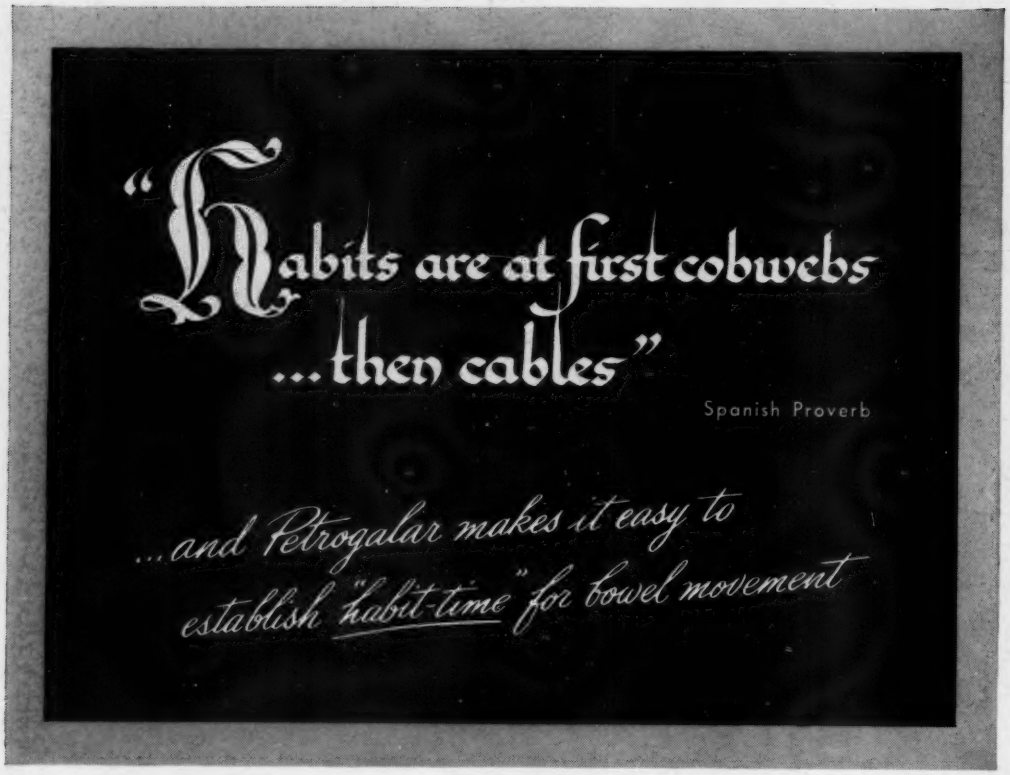
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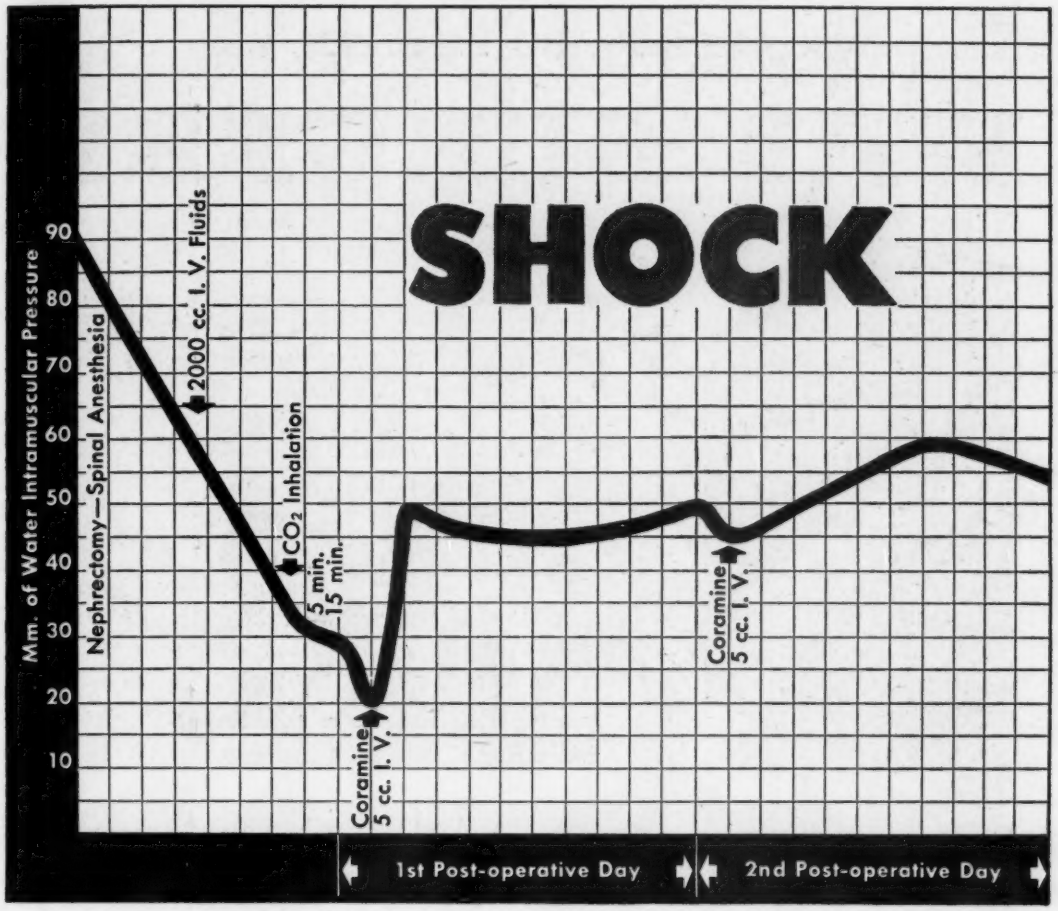

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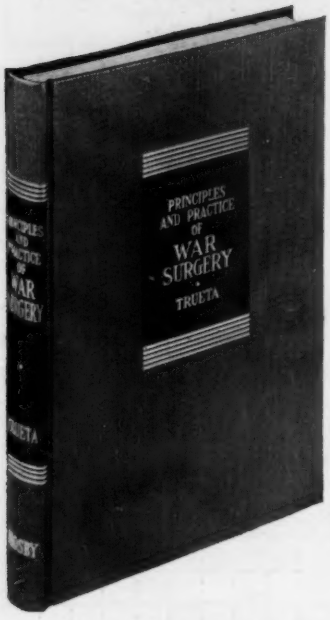

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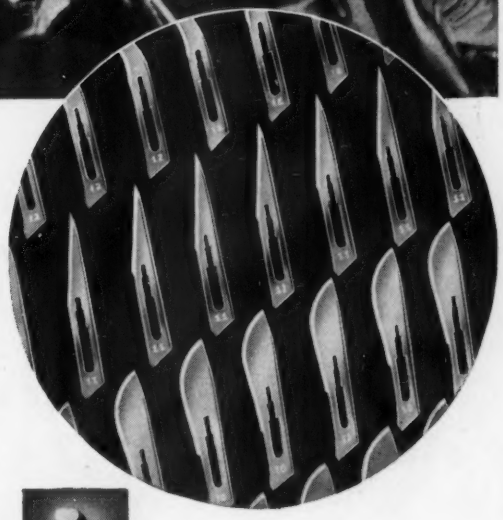

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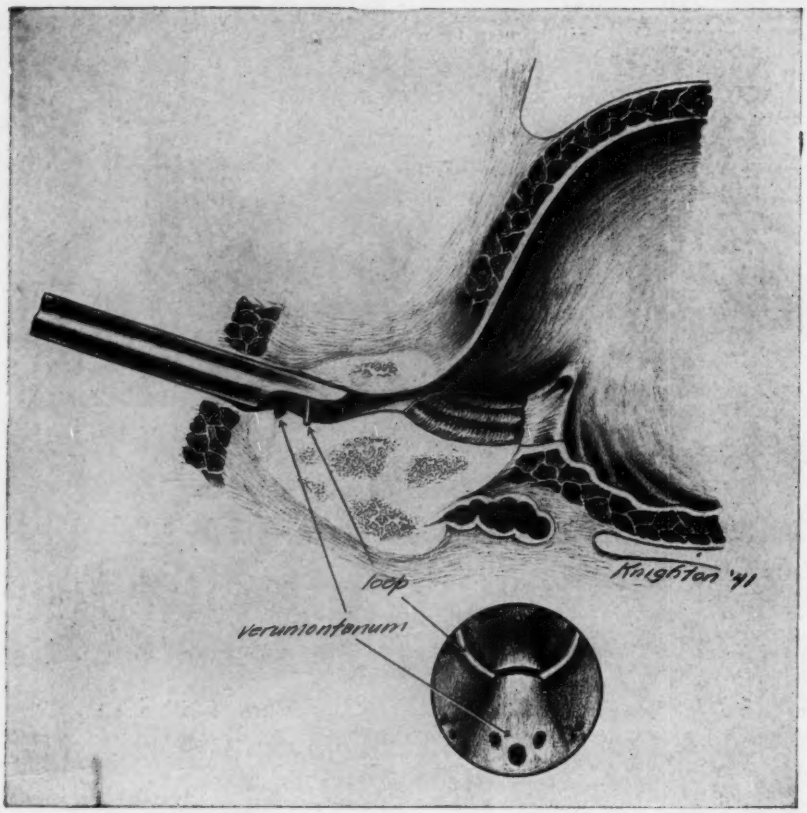

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(From the Department of Surgery, University of Michigan)

TOTAL gastrectomy implies the complete removal of the stomach with a segment of the esophagus and duodenum. Connor[7] performed the first total gastrectomy upon man in 1884. His patient did not survive the operation. Thirteen years later, Schlatter[27] reported the first successful case. In the years that have followed little enthusiasm was shown for what has generally been considered a formidable procedure. The mortality rate was 50 per cent (eighty-eight cases collected by Roeder, in 1933). The implication that the patient might survive the operation only to be relegated to a life of invalidism has further deterred surgeons from accepting this procedure in the treatment of gastric neoplasms. It was first thought that following this operation the patient would be forced to subsist on predigested foods and others have predicted that pernicious anemia would be an invariable sequel.

Recent reports[1, 2, 6, 8, 14, 17, 18, 20, 23, 33] indicate that the operation is now being performed with increasing frequency. It is therefore apparent that a knowledge of the effect of total gastrectomy upon nutrition and hematopoiesis is of practical importance.

Few studies have been made on digestion in man after gastrectomy and the findings have been conflicting.[12, 13, 15, 30] Since 1937, twenty-nine complete gastrectomies have been performed at the University of Michigan Hospital. Twenty-four of these patients survived the operation and have provided an opportunity for observations of the essential

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roles of the stomach in man. It is surprising how little their lives have been changed. A recent communication received from one of them reads: "I have continued to gain strength and have now gained thirty-three pounds. I am able to eat everything and am no longer troubled with indigestion."

This patient was operated upon Aug. 30, 1940, for an adenocarcinoma of the cardiac end of the stomach and was well thirty months later. Another patient, in his third postoperative year, was recently hospitalized for metabolic studies. He had gained twenty pounds and was able to take a 2,500 calorie diet in three regular meals without discomfort. There are several others who eat with little restriction in quantity or quality. Troublesome symptoms occurring early in the convalescence are related to the quantity of food ingested. These symptoms usually diminish rapidly as the postoperative period progresses. One patient, followed for nearly five years (longer than any case previously reported), is in good nutrition and has an excellent prognosis. Her case history follows.

R. B., a woman aged 40 years, was admitted to the University Hospital June 10, 1938. Her complaints were related to three episodes of hematemesis, melena, headache, weakness, and palpitation. She had been well until fifteen months prior to admission when she had experienced rather sudden vomiting of large amounts of grossly bloody material without premonitory signs. A second similar experience did not follow until nine months later during which time the patient had been quite well. Recovery was spontaneous and she was getting along well until three weeks prior to admission when the third episode supervened. Following this attack there were residual weakness, palpitation, and shortness of breath. There were few symptoms to suggest peptic ulcer and the patient had been able to tolerate all foods. There was no weight loss.

The physical examination revealed no abnormality other than a nodular enlargement of the fundus of a soft, movable uterus.

The laboratory findings were as follows: Hemoglobin (Sahli), 58 per cent; R.B.C., 4,400,000; W.B.C., 6,700; Kahn (blood), negative; serum proteins—total, 4.9; albumin, 3.0; globulin, 1.6.

TABLE I

GASTRIC ANALYSIS WITH HISTAMINE

	FREE	COMBINED
Fasting	22	8
15 min.	16	8
30 min.	34	6
45 min.	28	6
60 min.	32	6

Roentgenographic Examination.—Eight serial films demonstrated a filling defect, presumably neoplastic in origin, involving the lesser curvature and upper portion of the body of the stomach. One large fleck was interpreted as ulceration within the neoplasm (Fig. 1).

Peritoneoscopic examination was carried out June 15, 1938. Observations were excellent. There was no evidence of carcinomatosis, ascites, or hepatic metastases. The gastric neoplasm could not be seen with transillumination of the stomach. A large fibroid was visualized on the anterior wall of the uterus. Five days were then

spent in preparing the patient for operation. The hypoproteinemia was corrected with transfusions of blood. The stomach was carefully washed daily, vitamin supplements and hydrochloric acid were included in the diet, and measures were directed toward improvement of oral hygiene. Operability of the lesion seemed quite dubious.

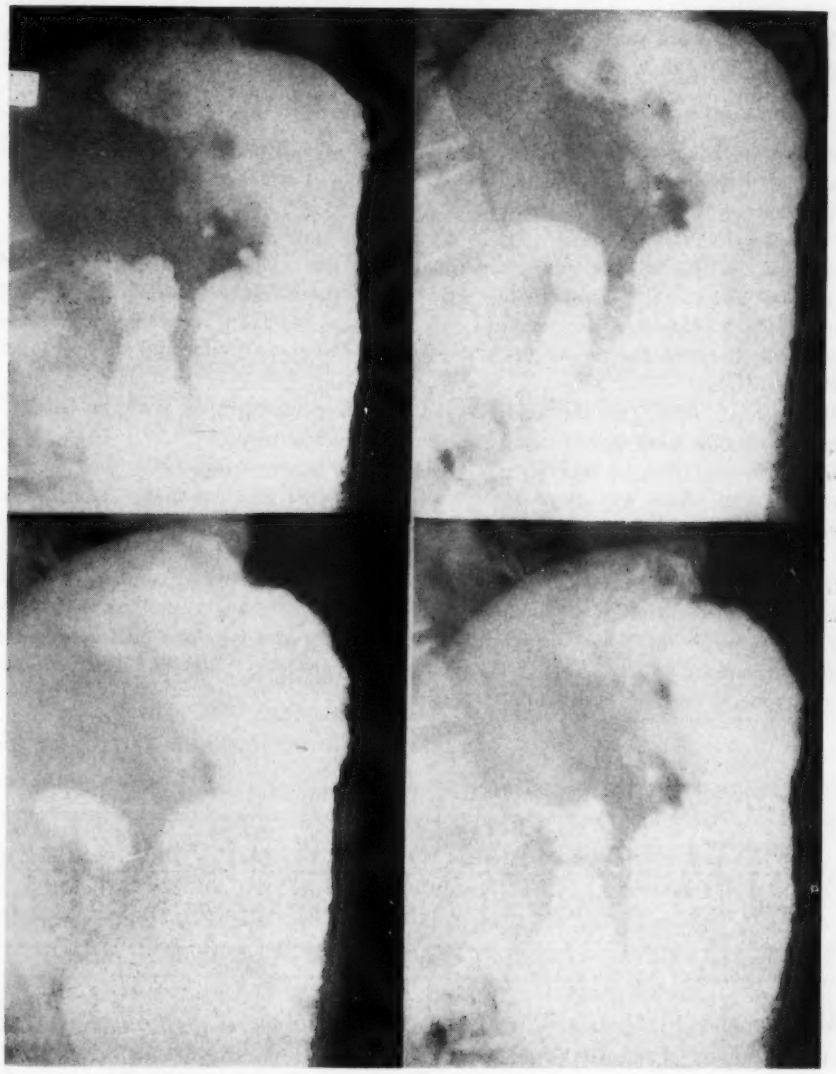


Fig. 1.—Serial films demonstrate a constant filling defect in the proximal lesser curvature of the stomach. One large ulcer fleck is visualized indicating ulceration within a large gastric neoplasm.

Operation.—On June 20, 1938, under spinal anesthesia, operation was performed (H. K. R.). On the lesser curvature of the stomach, in proximity to the esophagus, a peculiar dumbbell-shaped mass could be palpated. The mass consisted of two portions measuring approximately 3 by 4 cm., and extended to within 1 or 2 cm. of the esophagus. There were no palpable regional metastases but the extensive involvement of the proximal stomach precluded a partial gastrectomy. A total resection was therefore performed. The blood supply was divided along both curvatures beginning at the duodenum and extending to the esophagus. The duodenum was then divided and the stomach drawn upward to produce traction upon the intra-

abdominal esophagus. A loop of proximal jejunum was brought up through the transverse mesocolon and an esophagojejunostomy completed with two layers of interrupted fine silk sutures. The esophagus was not transected until the first row of sutures was in place. The peritoneum of the under surface of the diaphragm was utilized in buttressing and reinforcing the anastomosis. A complementary enteroenterostomy was made approximately 8 cm. below the previous anastomosis. A jejunostomy tube was placed in the efferent loop just below the mesocolon and brought out through a stab wound, lateral to the midline incision. The patient left the operating room in good condition and reacted promptly after returning to the ward.

Pathologic Diagnosis.—"A large neurofibroma of Schwannoma type. It is a well encapsulated, expansively growing neoplasm. The neoplasm will recur if not entirely removed." (Dr. C. V. Weller.)

Postoperative Course.—The patient's condition was excellent at all times. Jejunostomy feedings were begun after twenty-four hours and the patient was allowed up on her fourteenth postoperative day. The enterostomy healed promptly after removal of the tube. X-ray examination, on July 12, 1938, showed a satisfactory anastomosis between the esophagus and jejunum. She was living and well 56 months after operation.

In May of 1942 (at the end of the fourth postoperative year) a series of metabolic studies were begun using this patient as a subject.

Metabolism of Protein and Fat Following Total Gastrectomy.—She was placed on a weighed diet which was given for a three-day period (nine meals). The first and the ninth meal were "tagged" with carmine given orally. Collection of the feces was begun when the dye first appeared in the stool and stopped at the second appearance of the dye. The three-day collection was then dried and total nitrogen and total fat determinations were made.

The dry weight of the three-day stool was 62 Gm. and the total nitrogen content (Kjeldahl) was 2.34 Gm. The intake during the three-day diet had been carefully weighed and was as shown in Table II.

TABLE II

INTAKE DURING THREE-DAY DIET

INTAKE	PROTEIN (GM.)	FAT (GM.)	CARBOHYDRATE (GM.)
1st day	68	89	250
2nd day	70	105	250
3rd day	62	72	235
Total	200	266	735

Most of the nitrogen arising from the catabolism of protein is excreted in the urine. A small fraction is eliminated through the secretion of the intestinal mucosa. This is *metabolic nitrogen* and may be estimated from the nitrogen of the feces on a nitrogen-free diet. In man 0.5 to 1.5 Gm. are excreted in this way daily. In order to determine the proportion of a given amount of protein which has undergone digestion and absorption, the total nitrogen content of the ingested protein is determined and the following formula used:

Food Nitrogen – (Stool N – Metabolic N) = Absorbed Nitrogen

The percentage of absorbed nitrogen is known as the *coefficient of digestibility*. The proteins of food contain 16 per cent nitrogen. Therefore, the 200 Gm. of ingested protein over the three-day period contained 12.5 Gm. of nitrogen. Employing this formula:

Food Nitrogen		Stool N		Metabolic N		Absorbed N
$\frac{200}{16}$	= 12.5 –	(2.34	–	1.0)	=	11.6 Gm.

The coefficient of digestibility of the protein in the three-day diet is 89.2 per cent. Of the various proteins those of animal origin are the most digestible (95 per cent). The digestibility of the protein in fruits and nuts is low and that of the proteins of legumes and of potatoes is around 80 per cent. The coefficient of 89.2 per cent is a normal figure for the protein contained in this diet.[4]

These results serve to support the clinical observation that patients are able to keep in good nutrition following total gastrectomy. As far as protein digestion is concerned it appears that the stomach does not play an essential role and this function may adequately be taken over by the trypsin of the pancreas and the erepsin of the small intestine.

This patient ingested 266 Gm. of fat in the three-day period. Total fat determinations (Saxlet) were done. There were 4.5 Gm. of total fat or 7.3 per cent of the dry weight. According to Bodansky and Bodansky[5] this value falls within the normal range of percentage of fat in dry feces. These findings are in accord with the general knowledge that gastric lipase is a weak fat-splitting enzyme, of little practical importance in adults. It is soon rendered inactive as the acidity of the gastric contents rises during digestion and any action it may have is exerted only upon fats in a state of very fine emulsion. Many question if this enzyme in the stomach has any real digestive value. Therefore, it is not surprising that complete gastrectomy does not interfere with this particular phase of nutrition.

Gavrila and Danicico,[13] from their study of thirteen patients upon whom gastroenterostomy and various types of *partial* gastrectomy had been performed, report that the digestion of fat was impaired in all the patients. They attributed this deficit to a pancreatic insufficiency following partial resection of the stomach. The increased motility of the gastrointestinal tract early in the postoperative period appears to be a much more likely cause. In nearly all cases of resection of the stomach the passage of food may be greatly accelerated early in the patient's convalescence. In four patients that we have followed for several years there have been no errors in fat metabolism.

Hematopoiesis Following Total Gastrectomy.—It is increasingly apparent that gastrectomy may be performed without any great fear of undue consequences as far as the factor of hematopoiesis is concerned. Fig. 2 shows the results of complete blood examinations over a four-year period following complete gastrectomy. The mean corpuscular volume has consistently remained below macrocytic levels. The original hypothesis of Castle implied that gastrectomy might well be followed by pernicious anemia. However, clinical experience indicates that this

complication is rarely, if ever, encountered. Furthermore, many experiments have been performed on a wide variety of laboratory animals in an effort to produce pernicious anemia of agastric genesis. No one has been able to produce the typical changes in the bone marrow and peripheral blood associated with hyperchromic macrocytic (pernicious) anemia following total gastrectomy in animals. The experiments of: Mann (1929), Ivy, Morgan, and Farrell (1931), Mann and Graham (1932), Aron and Bauer (1933), Mullenix, Dragstedt, and Bradley (1933), Doulcine and Bondarenko (1934), Ducuing, Miletzky, and Soula (1936), Shumacker and Wintrobe (1935), Petri and Jensenius (1941), Singer (1935), Kohno (1935) have all given similar results in this regard.

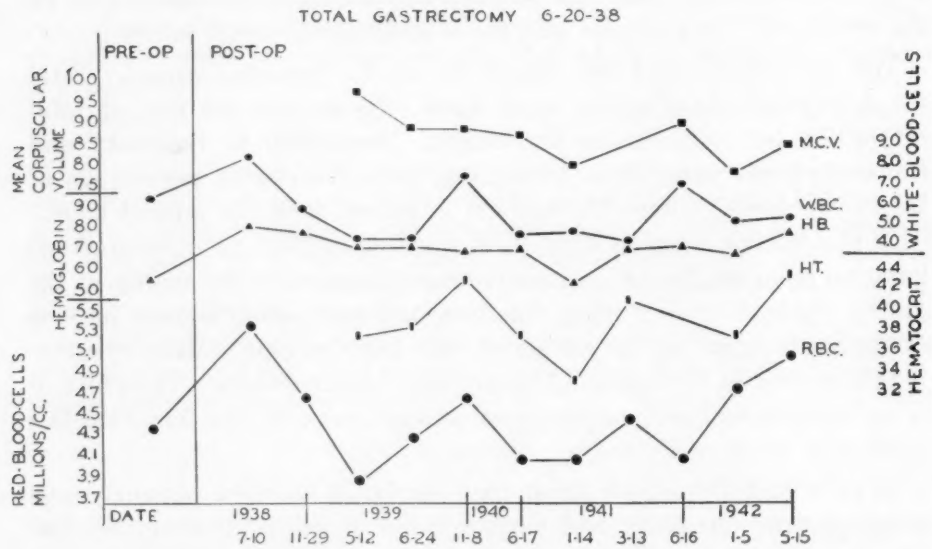


Fig. 2.—Illustrating blood findings over a four-year period. The mean corpuscular volume has consistently remained below macrocytic levels. Values between 110 and 140 are generally obtained in pernicious anemia. Low hemoglobin levels have invariably been associated with the failure to take ferrous iron. Elevation in hemoglobin level has been a consistent response to the administration of iron.

From a study of 800 partial gastrectomies, Walton[32] was unable to detect alterations in hematopoiesis. Sturgis and Goldhamer[31] were unable to collect more than three cases of macrocytic anemia following gastrectomy from the total group of anemias seen at the Simpson Memorial Institute at the University of Michigan. In our series of twenty-nine total gastrectomies, four have now survived the operation longer than two years. Careful blood examinations on these four patients do not show macrocytic anemia. However, many of the patients do develop an anemia although of the hypochromic microcytic type that is commonly associated with iron deficiency. Improvement is consistently apparent from the administration of hydrochloric acid with the diet or ferrous iron. The hemoglobin level will remain satisfactory as

long as the patient takes ferrous iron one week out of each month. Late in 1940, iron was not taken by this patient (Fig. 2) for two months and on Jan. 14, 1941, the hemoglobin level was 56 per cent (Sahli). However, when iron therapy was resumed, a satisfactory response was obtained.

This iron deficiency anemia results from alterations in the physiologic principles controlling the absorption of iron. Under normal conditions, the inorganic iron of the food which is in the ferric state, is converted by the HCl to the ferrous form. Ferrous iron is the only form in which it can be absorbed by the alimentary tract.[4] It is likewise now known that the organic form of iron in foods is not available for absorption as it is not released by peptic or tryptic ferments. Animals fed dipyridyl, for example, become anemic since the inorganic iron is rendered insoluble. In certain anemias accompanied by the absence of HCl, compounds of ferrous iron (sulfate, chloride, carbonate) are specific in their effects. It has been shown by Castle and associates that in hypochromic anemia a daily dose of 32 mg. of iron and ammonium

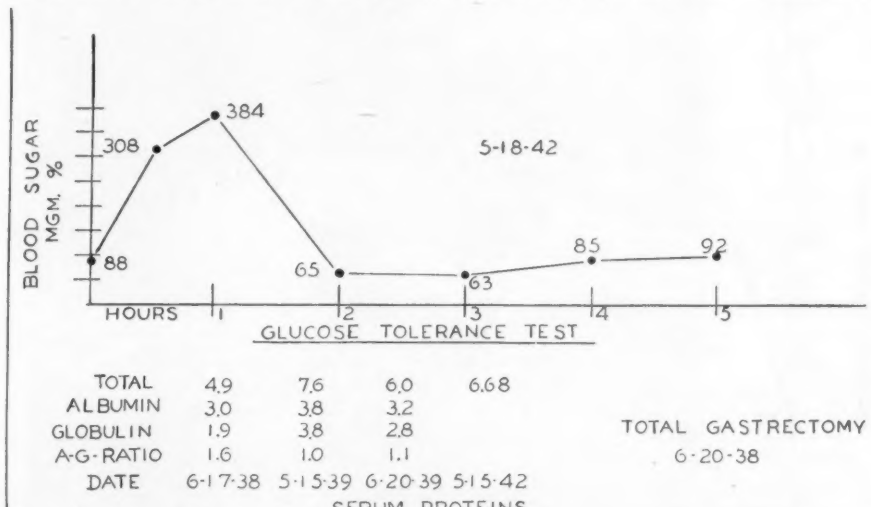


Fig. 3.—Illustrating glucose tolerance curve following total gastrectomy. These curves differ from normal in certain respects. The initial phase of hyperglycemia is more pronounced and has been followed in the cases studied by a rapid fall to levels approaching hypoglycemia. The lowest levels are usually observed in the third hour and are followed by gradual recovery to fasting levels in the fourth and fifth hours.

citrate, administered subcutaneously, is utilized completely in the formation of hemoglobin. It was also shown that 32 mg. of iron administered in this way is equal to 1,000 mg. given by mouth.[4] This further demonstrates that only a very small proportion of ferric iron is converted into the absorbable (ferrous) form in the alimentary tract under normal conditions. Therefore, after total gastrectomy, the inorganic iron normally contained in the richly iron-containing foods is not available for absorption until it has been changed into the ferrous form. This requires the presence of the hydrogen ion. Hydrochloric acid may be

given with the diet. In most of our patients, 0.32 Gm. of ferrous sulfate taken three times a day for one week out of each month has proved to be efficacious in preventing a hypochromic microcytic anemia.

Carbohydrate Metabolism.—Qualitative information concerning carbohydrate metabolism may be obtained from glucose tolerance studies. Glucose tolerance curves following total gastrectomy differ from normal values in the following respects: The initial phase of hyperglycemia is more pronounced and has been followed in the cases studied by a rapid fall to hypoglycemic levels. The lowest levels of blood sugar have been observed during the third hour and are usually followed by a gradual recovery to fasting levels in the fourth and fifth hours (Figs. 3 and 4). These changes may be attributed to alterations in absorption, utilization or rate of deposition of glucose. Inasmuch as the *intravenous* glucose tolerance test in these patients gives a perfectly normal curve, it is apparent that these changes are a result of an increase in rate of absorption of glucose following total gastrectomy.

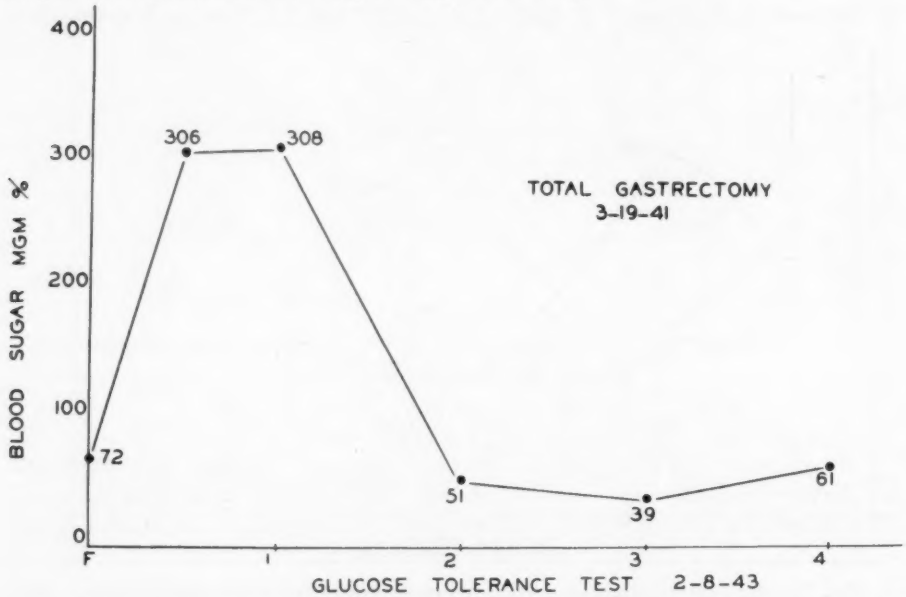
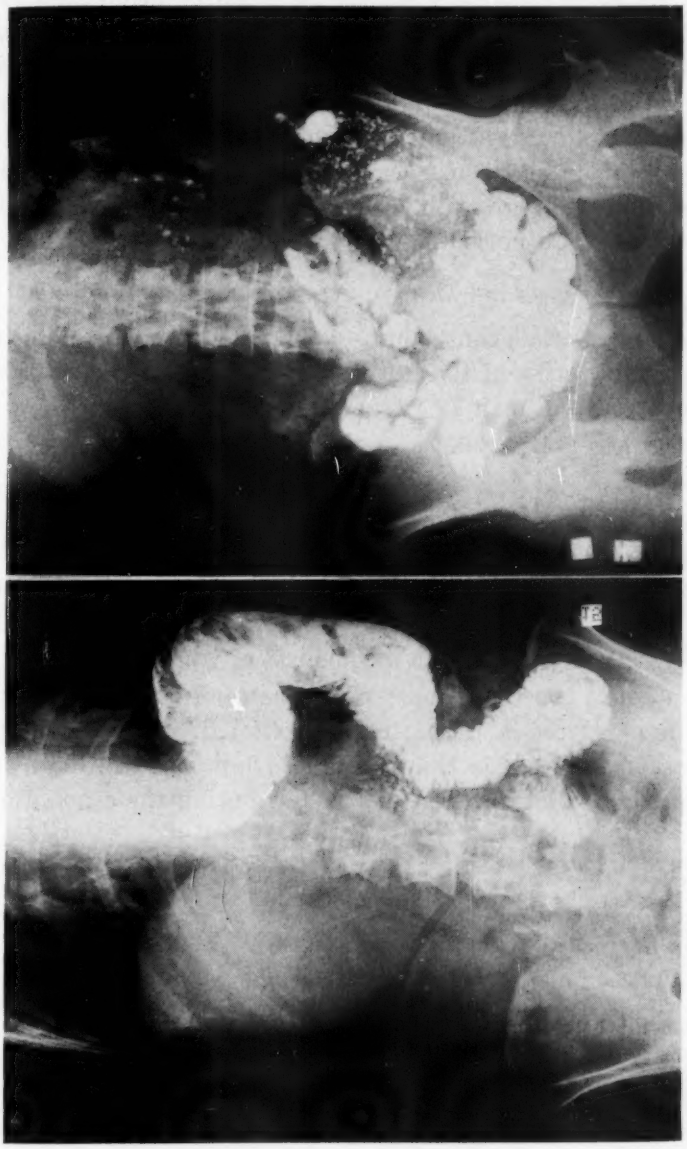


Fig. 4.—Illustrating hypoglycemia occurring during a glucose tolerance study (1.75 Gm. per kilogram of ideal body weight given orally). During the third hour the patient experienced definite symptoms of hypoglycemia.

It is noted in Fig. 4 that this patient's blood sugar was 39 during the third hour. This approaches convulsive levels and the patient was distinctly uncomfortable. These low blood sugar values may produce the typical signs of the hypoglycemia syndrome. It is presumably due to hyperinsulinism, which is secondary to the primary phase of hyperglycemia. This physiologic mechanism might well explain attacks of weakness, vertigo, and palpitation occasionally observed following partial gastrectomy. Rapid emptying of the stomach through large anastomoses (Polya type) will facilitate the rapid absorption of glucose and

may be followed by secondary hyperinsulinism and hypoglycemia. High protein, low carbohydrate diets are effective in preventing postprandial abnormalities in the blood sugar levels.



B.

A.

Fig. 5.—Roentgenograms after the ingestion of barium show enlargement of the distal jejunal loop (*A*). A five-hour film shows normal progression of the barium column through the small intestine (*B*). There is no evidence of barium in the colon; carmine administered orally does not appear in the stool for thirty-six hours.

Motility of the Gastrointestinal Tract Following Total Gastrectomy.—Gastroenterostomy, partial gastrectomy, and total gastrectomy may all produce transient increased motility of the gastrointestinal tract. Ingested powdered charcoal may appear in the stool in twelve hours.[12] When digestive deficits have been observed following gastric operation, it is reasonable to assume that they are a result of the increased motility. In the patients that we have followed, this phenomenon has been of temporary significance. Fig. 5*A* illustrates the changes occurring in the

distal loop of jejunum over a four-year period, following total gastrectomy. The storing capacity of the stomach is simulated. Fig. 5*B* illustrates the progress of the barium meal five hours after oral ingestion. There is no evidence of barium in the colon, which indicates a slight decrease in motility. Carmine administered orally does not appear in the stool for thirty-six hours. The vagus nerves are almost invariably sacrificed in the course of total gastrectomy. Inasmuch as they are predominantly motor, gastrointestinal motility may eventually be decreased through this mechanism. Another patient twenty-four months after operation showed progression of barium at one, three, and five hours, slightly slower than normal.

SUMMARY AND CONCLUSIONS

1. The mortality rate following total gastrectomy is not prohibitive. There have been two deaths in the last nineteen consecutive operations. One of these occurred in a man 79 years old.

2. The stomach does not play an essential role in the digestion of fats and protein.

3. There is no experimental evidence that removal of the stomach will produce pernicious anemia. Clinical experience likewise indicates that primary anemia is rarely encountered following various gastric operations.

4. Gastrectomy interferes with the metabolism of iron.

5. The absorption of glucose is more rapid than normal. This results in a transient hyperglycemia phase that is followed by hypoglycemia. This latter phase may produce characteristic symptoms. A high protein, low carbohydrate diet is efficacious in preventing these abnormalities.

6. A patient is reported who survived total gastrectomy four years and seven months. She is living and well.

7. Motility is decreased rather than increased. This may be due to intra-abdominal section of the vagus nerves.

We acknowledge the helpful collaboration of Miss Sue Biethan in preparing the bibliography.

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INTESTINAL STRANGULATING OBSTRUCTION WITH NEGATIVE ROENTGENOLOGIC FINDINGS*

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THE difficulties of recognizing internal intestinal strangulating obstruction are well known. Although the pain is usually colicky in nature, in some patients it is sharp and continuous, simulating that of perforated peptic ulcer, twisted ovarian cyst, acute pelvic inflammatory disease, or mesenteric infarction or thrombosis. The venous return from the segment of bowel is often occluded first so that the involved loop quickly fills with blood, usually replacing any gas which may be present in the affected loop. The physical findings in this group of patients simulate those of peritonitis rather than simple intestinal obstruction. The irritating serosanguineous fluid in the peritoneal cavity produces tenderness, rigidity, and an inhibition of peristalsis. While patients with acute strangulating intestinal obstruction may present symptoms closely resembling those of simple obstruction, the presence of fever, tenderness, rigidity, a palpable abdominal mass, or leucocytosis is usually evidence that the blood supply has been interrupted.

Since Schwartz,[1] Assmann,[2] Case,[3] and others emphasized the positive roentgenologic findings of intestinal obstruction, little has been mentioned about the possibility of negative findings, particularly in strangulating obstructions. Rabwin[4] mentioned two such patients in whom no evidence of obstruction appeared on x-ray examination.

We have observed several patients with minimal roentgenologic evidence of obstruction, characterized by the presence of a small accumulation of gas in the proximal bowel, even though several feet of small intestine were gangrenous. We have seen four patients with acute strangulating intestinal obstruction, two of whom showed no roentgenologic evidence of obstruction and two of whom showed changes which might be considered questionable. In the latter group such changes as appeared were thought to represent signs of paralytic ileus inasmuch as it was believed that peritonitis from some other cause might be present.

CASE REPORTS

Strangulating Obstruction With Negative Roentgenologic Findings

CASE 1.—K. W., a housewife, 66 years of age, had had a hysterectomy ten years prior to the present illness. She presented a history of cramplike pain at the onset

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which quickly became continuous in type and spread over the entire abdomen. This was followed by constipation and the vomiting of bile-stained fluid. The physician in attendance observed her at home for twenty-four hours. On entry her temperature was 37.5° C., pulse rate 110, respirations 24. The abdomen was tender and rigid throughout the lower portion and no peristaltic activity was heard. The blood count showed 92 per cent hemoglobin; red blood cells, 4,420,000; white blood cells, 14,600; polymorphonuclear leucocytes, 78 per cent. Her pain and findings increased. Thirty-six hours after the onset of her illness, roentgenograms of her abdomen showed the stomach and first portion of the duodenum to be distended with gas, but there was no evidence of gaseous distention of the small intestine (Fig. 1). At operation immediately thereafter, approximately four feet of gangrenous lower ileum were found. The strangulation was caused by a narrow adhesive band running from the posterior parietal wall on the right side to the region of the broad ligament. This band had tightly encased the bowel and its mesenteric blood supply, causing complete obstruction to both. The gangrenous loop of bowel was heavy, filled with sanguineous fluid, and there was a large amount of serosanguineous fluid in the peritoneal cavity.

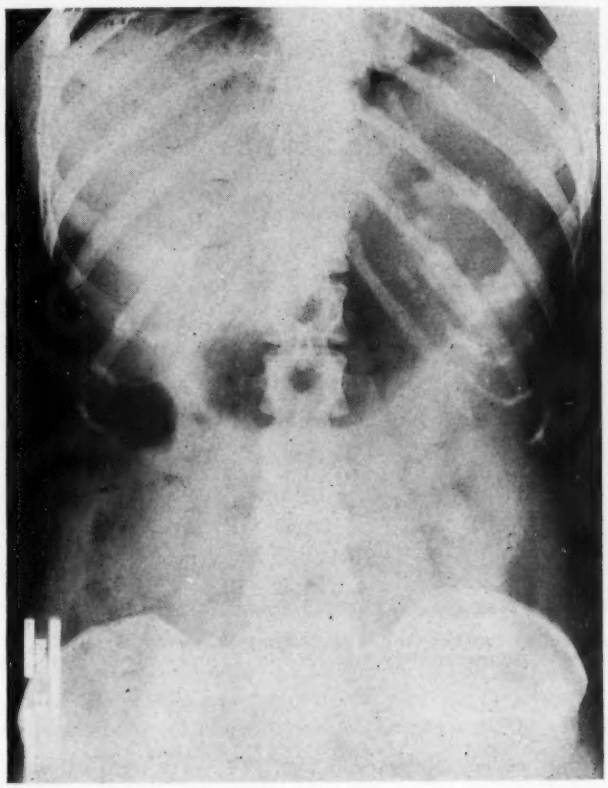

Fig. 1.—Roentgenogram showing gas in the stomach and duodenum but none in the small intestine; four feet of gangrenous ileum were resected in this patient.

CASE 2.—B. S., a housewife, 44 years of age, had had an appendectomy through a right rectus incision fourteen years previously, and a right salpingo-oophorectomy eight years before this illness. Sixteen hours before entry to the hospital she had sudden, severe, progressive pain in the mid-portion of the abdomen. She vomited upper intestinal contents only once. On entry, her temperature was 37.9° C., pulse rate 100, and respirations 20. The abdomen was not distended and a mass could be

outlined in the left lower quadrant. Mild tenderness and rigidity were present throughout the lower half of the abdomen and no peristalsis was heard. Blood count showed 78 per cent hemoglobin; red blood cells, 3,860,000; white blood cells, 18,600; polymorphonuclear leucocytes, 84 per cent; lymphocytes, 14 per cent; monocytes, 2 per cent. Shortly before operation a roentgenogram (Fig. 2) showed the presence of gas only in the large intestine. There was no evidence of distention or accumulation of gas or fluid in the small bowel. At operation a moderate amount of bloody fluid was found in the peritoneal cavity. A very tight adhesive band ran from the mesentery of the terminal ileum to the left parietal wall and completely constricted the lumen of the bowel and its blood supply. Approximately five feet of gangrenous lower jejunum and upper ileum were resected.

Fig. 2.—Roentgenogram showing gas present in the colon; there is no distention of the small bowel. Approximately five feet of gangrenous jejunum and ileum were encountered at operation.

Strangulating Obstruction With Questionable Roentgenologic Findings

CASE 3.—O. C., a woman, 48 years of age, had had a right salpingo-oophorectomy and appendectomy sixteen years previously. She entered the hospital after twenty-eight hours of severe pain, which was colicky at the onset but soon became continuous in character. She vomited several times and had one small normal bowel movement. Her temperature was 38.4° C., pulse rate 120, respirations 24. The abdomen was slightly distended and peristalsis diminished. A mass palpated in the lower abdomen on bimanual pelvic examination was thought to be an ovarian cyst twisted on its pedicle. The blood count showed 96 per cent hemoglobin; red blood cells, 4,640,000; white blood cells, 22,400; polymorphonuclear leucocytes, 92 per cent; lymphocytes, 8 per cent. The roentgenogram (Fig. 3) showed evidence of gas in the stomach,

duodenum, splenic flexure, and sigmoid colon. A centrally placed loop of bowel showed a small amount of gas running transversely. These findings were interpreted as being consistent with paralytic ileus and the grayness of the film suggested free fluid. Laparotomy showed a large amount of bloody fluid in the peritoneal cavity. An adhesive band running between the mesenteries of the loops of small intestine had caused the strangulation of six feet of ileum.

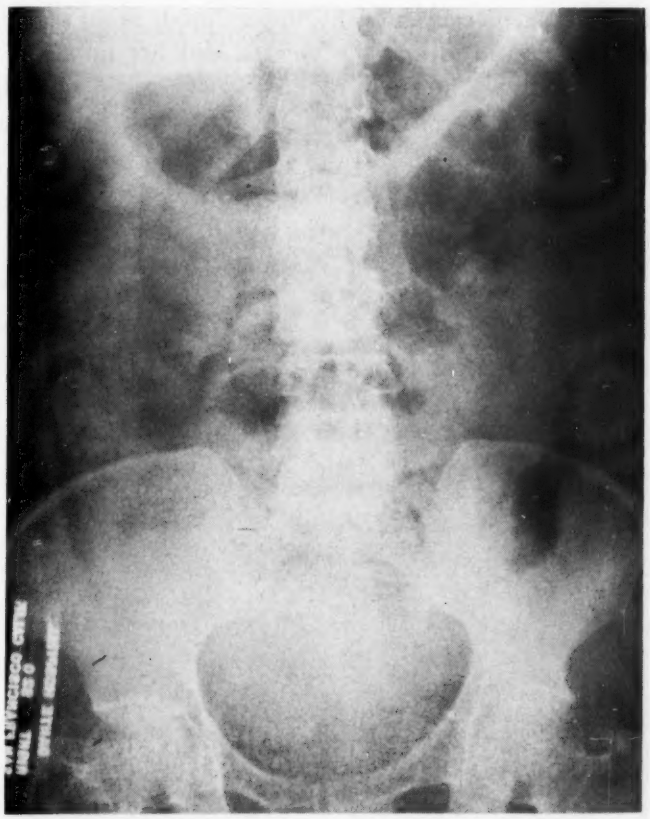

Fig. 3.—Roentgenogram interpreted as showing no evidence of mechanical obstruction. Six feet of ileum were strangulated by adhesive band.

CASE 4.—L. L., a man, 34 years of age, had had an appendectomy through a right rectus incision six years previously. Twelve hours before entry to the hospital, severe colicky pain began in the right lower quadrant followed by vomiting and constipation. His temperature was 38.5° C., pulse rate 110, and respirations 28. The abdomen was not distended, slight guarding and tenderness were present over the right side. Peristalsis was hyperactive, the sounds being high-pitched and metallic. Blood count showed 90 per cent hemoglobin; red blood cells, 4,620,000; white blood cells, 17,600; polymorphonuclear leucocytes, 88 per cent; lymphocytes 12 per cent. Roentgen examination (Fig. 4) showed gas in the stomach and colon. There was a loop of gas-filled bowel along the left lateral wall which was interpreted as being descending and sigmoid colon. At operation, eighteen inches of gangrenous lower jejunum were found, having been produced by an adhesive band. A moderate amount of bloody free fluid was encountered.

The interest aroused by these cases, with few or no roentgenologic evidences of obstruction in the plain film, stimulated experimental work in an attempt to explain its mechanism.

In 1933, Ochsner,[5] after tightly ligating loops of small intestine together with their blood supply, in dogs, reported that strangulating obstruction produced more marked accumulations of gas and fluid than were found in simple obstruction, and noted that the roentgenologic findings appeared earlier than in the simple type. Goehl, Lynch, Borman, and Wangensteen,[6] on the other hand, observed that roentgenologic evidence of intestinal obstruction did not appear so early in animals with strangulation as in those with simple obstruction. The same method of ligation as that employed by Ochsner was used, except

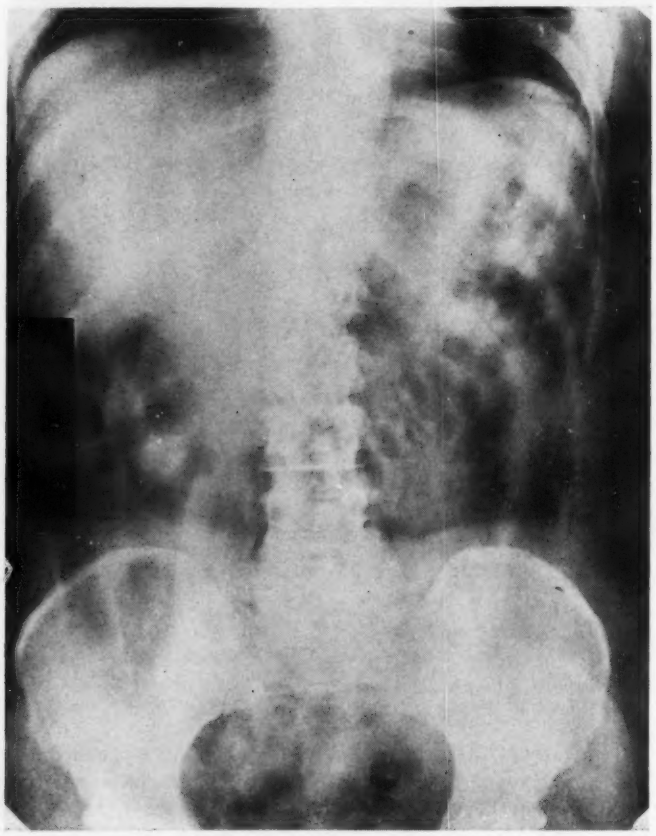

Fig. 4.—Roentgenogram showing questionable loop of distended small bowel or colon in the left flank. Eighteen inches of lower jejunum were strangulated by adhesion.

that varying degrees of strangulation were obtained. Carlson, Dvorak, Lynch, Borman, and Wangensteen,[7] after ligations of mesenteric vessels in dogs, concluded that, while roentgenographic evidence of gaseous distention is an early and a valuable sign of simple intestinal obstruction, it is of distinctly less value in strangulating obstruction or stasis caused by occlusion of the mesenteric vein. Hibbard, Swenson, and Levin[8] were unable to produce positive roentgenologic findings of obstruction after ligating mesenteric veins which drain long segments of small intestine. X-ray films taken after ligation of the superior mesenteric vein

draining one-half of the ileum and jejunum did not reveal the presence of gas, whereas films taken after the ligation of the mesenteric veins draining nearly 10 cm. of the ileum showed the presence of gas in three hours and fluid in five hours. In studying mesenteric occlusion as well as intestinal strangulation numerous observations have been made[9] on the effects of the ligation of arteries, veins, both arteries and veins, and the wall of the bowel, in various combinations.

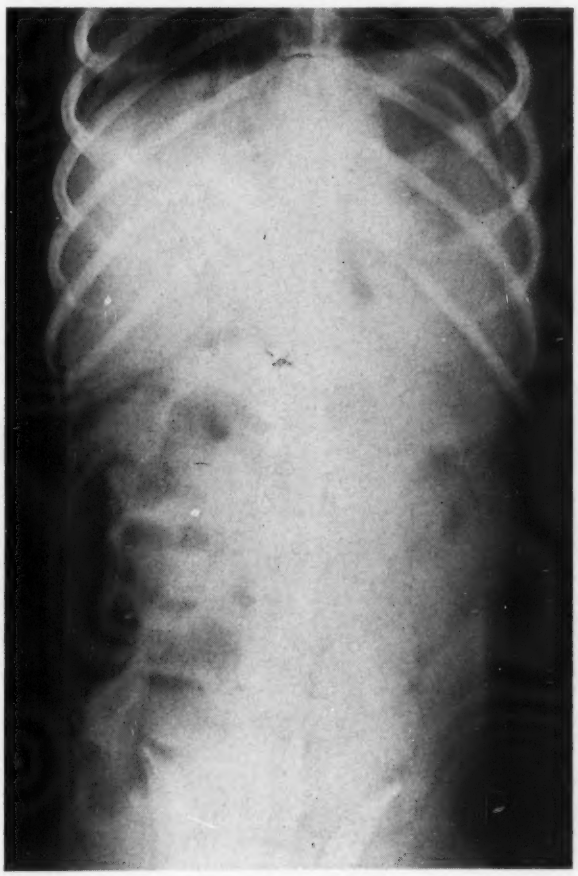

Fig. 5.—Roentgenogram showing gaseous distention of small intestine of dog following ligation of a segment of ileum and its blood supply.

EXPERIMENTAL METHODS

It occurred to us that, in order to simulate more closely the mechanism of internal strangulating obstruction caused by the slipping of a loop of bowel under a band or through an abnormal opening, in the human being, the gradual production of strangulation might be prefferable to ligation. The changes occurring when a loop of intestine and its blood supply are gradually constricted are venous engorgement, perivascular hemorrhage, venous stasis, edema, cyanosis, spasm of the affected loop of bowel, and hemorrhage into the lumen and the wall of the bowel. The mesentery becomes edematous so that the arterial

supply is also encroached upon at the neck of the constriction and the lumen of the bowel is occluded, thereby setting up a vicious cycle, until perforation and peritonitis take place or sufficient hemorrhage accumulates in a long segment to be an added factor in causing shock or death.

Accordingly, three groups of experiments (ten dogs each) were carried out in an attempt to determine the frequency of negative x-ray findings in strangulating obstructions.

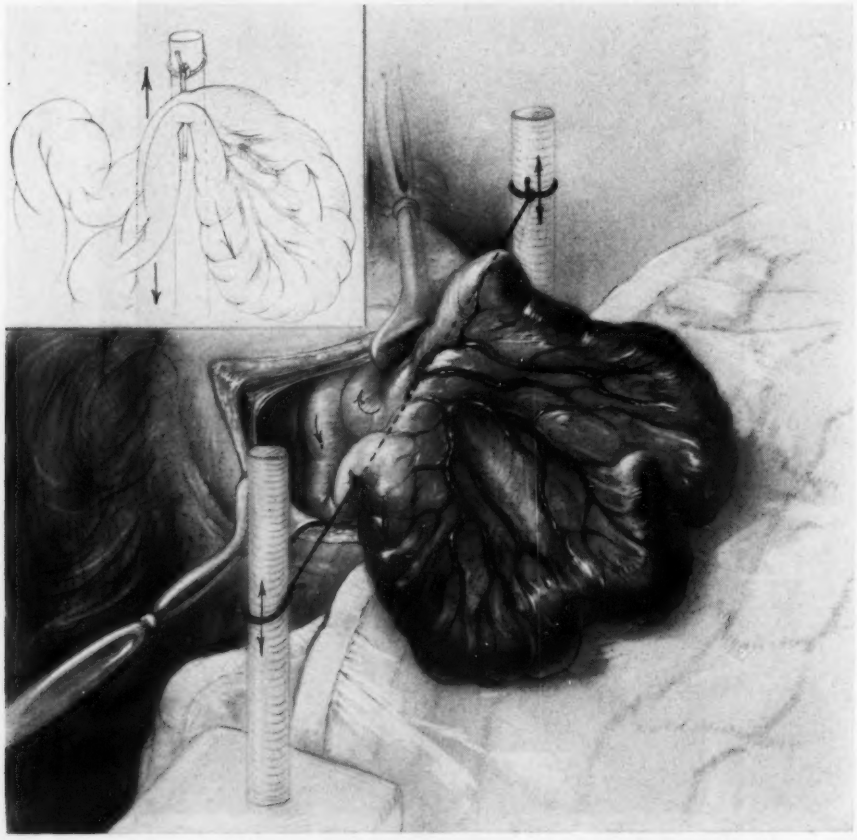

Fig. 6.—Drawing showing method of producing gradual strangulating obstruction.

Group I.—A loop of ileum, 40 cm. in length, with its blood supply, was ligated with stout cotton tape, approximately 75 cm. proximal to the ileocecal valve so as initially to occlude the lumen and its mesenteric circulation. This was carried out in an aseptic manner under ether anesthesia and the operative wound was closed. Anteroposterior films were then taken with the animal held at 60 degrees of the vertical position.

Results: In all of these dogs roentgenograms showed evidence of accumulation of gas and fluid proximal to the strangulation (Fig. 5) within ten hours, the earliest appearing at 2½ hours and the average

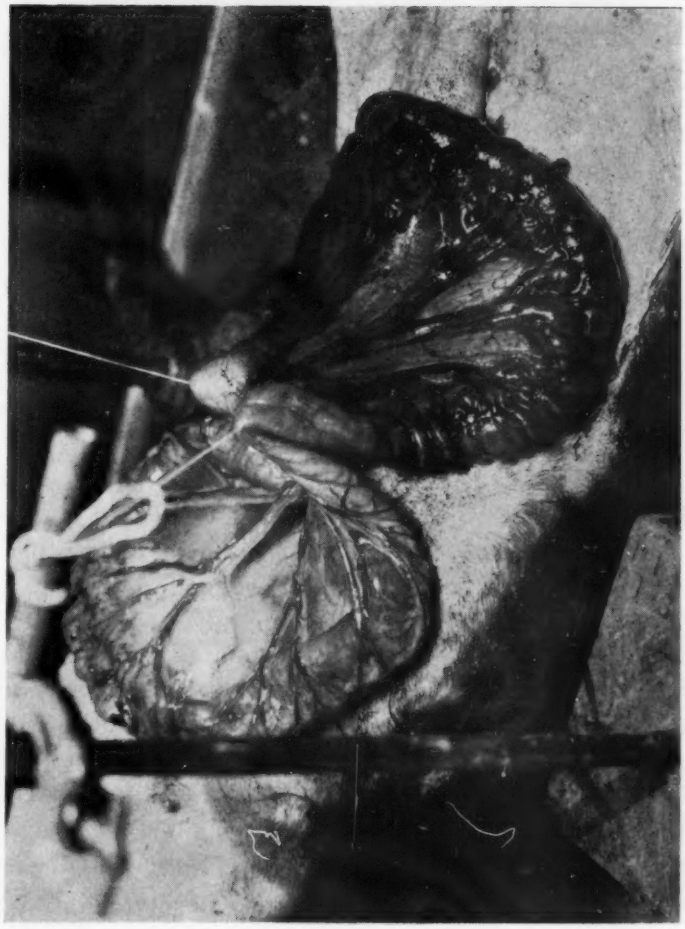

Fig. 7A.

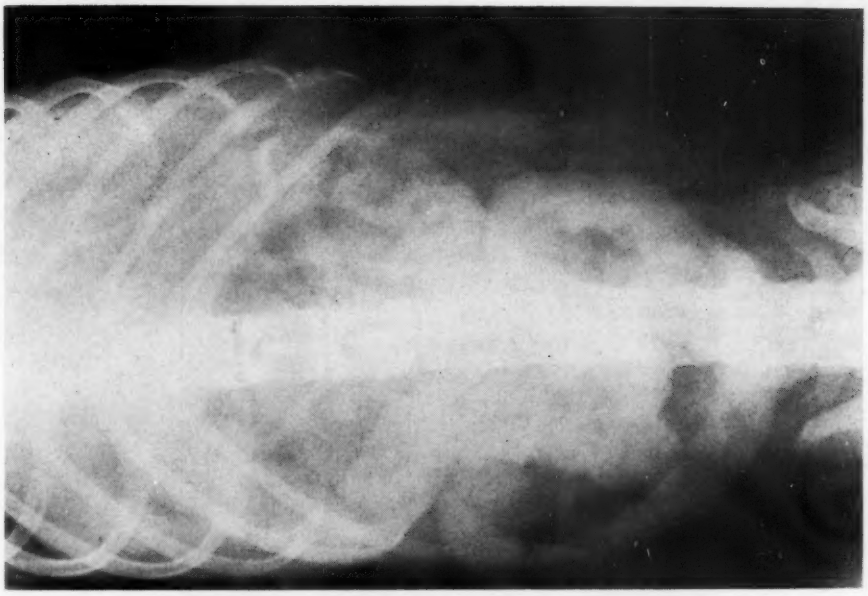

Fig. 7B.

Fig. 7A.—Photograph showing a loop of gangrenous ileum and proximal bowel for comparison.

Fig. 7B.—Roentgenogram showing absence of gaseous distention; note the accumulation of fluid in the exteriorized loops.

being approximately 6 hours. In all of the animals autopsies revealed distention due to the accumulation of gas and fluid proximal to the obstruction.

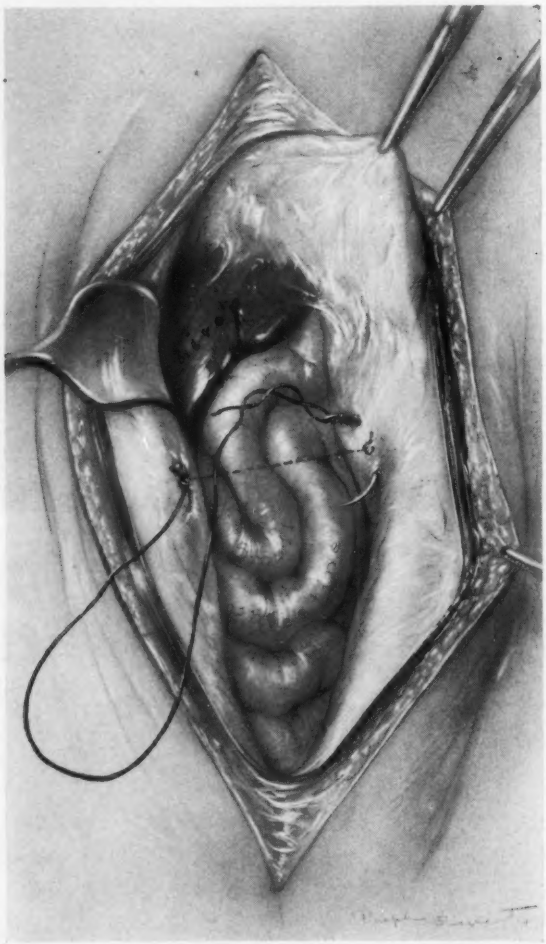

Fig. 8.—*A*, *B*, and *C*. Drawings showing the method of producing gradual strangulation aseptically.

Group II.—Under intravenous sodium pentobarbital anesthesia, supplemented as needed, a loop of ileum 40 cm. long with its mesentery was exteriorized over a linen string, the height of which could be regulated above the level of the anterior abdominal wall (Fig. 6). The loop of intestine was permitted to hang apronlike over the string onto the lower portion of the anterior abdominal wall. The height of the string was then adjusted to a level that would produce venous engorgement. The bowel was handled gently and kept warm with pads so as to minimize the inhibition of peristalsis as much as possible. This loop was observed as long as the dog could be prevented from going into shock, a period varying from 6 to 12 hours.

Results: In some of the dogs the arterial pulsations to the loops disappeared within 2½ hours and in some they continued for 6 hours, the

average being 3¾ hours. Anteroposterior x-ray films were taken within from 6 to 10 hours. Seven of the animals showed definite accumulations of gas as seen by the x-ray. In 3, however, no gaseous accumulation or distention was noted proximally to the obstruction. Fig. 7*A* shows a loop of gangrenous bowel produced in this manner and the immediately proximal loop placed cephalad for comparison. The collapsed state of the proximal loop of bowel can be noted and compared to the x-ray film (Fig. 7*B*) of this same animal which discloses no gaseous distention proximal to the obstruction. Great venous engorgement and tenseness, and gangrene of the involved loop are evident.

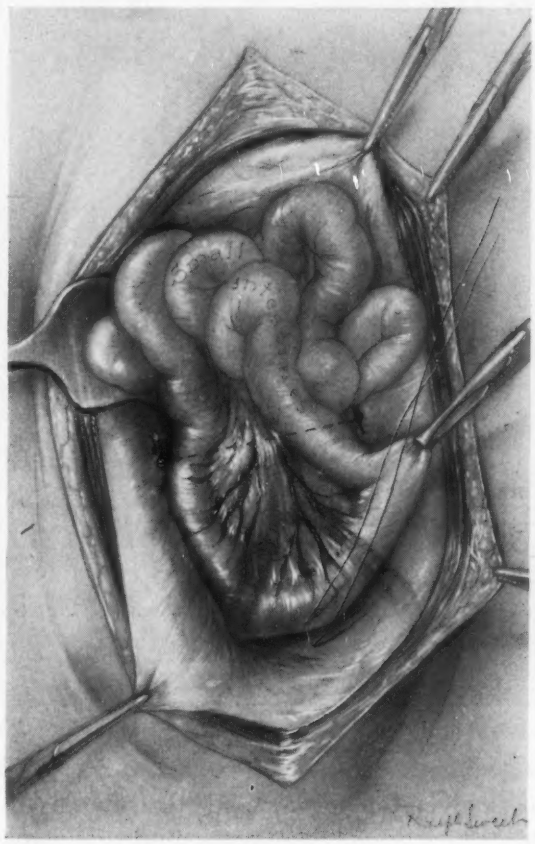

Fig. 8*B*.

Group III.—In order to produce intestinal strangulation in this manner but carry the observations over a longer period of time, the same effect was produced in 10 dogs by placing a similar loop of ileum over a stout linen suture, running transversely across the peritoneal cavity and anchored at the lateral border of the rectus sheath on each side (Figs. 8*A*, 8*B*, and 8*C*). This was done under ether anesthesia, with aseptic technique. The loop of ileum was then sutured to the retroperitoneal fascia anterior to the sacrum so that there would be no later

displacement. It was placed under sufficient tension that the string would cause engorgement of the venous return.

Results: The x-ray films of eight of the ten dogs showed evidence of obstruction as characterized by gaseous distention of the small bowel.

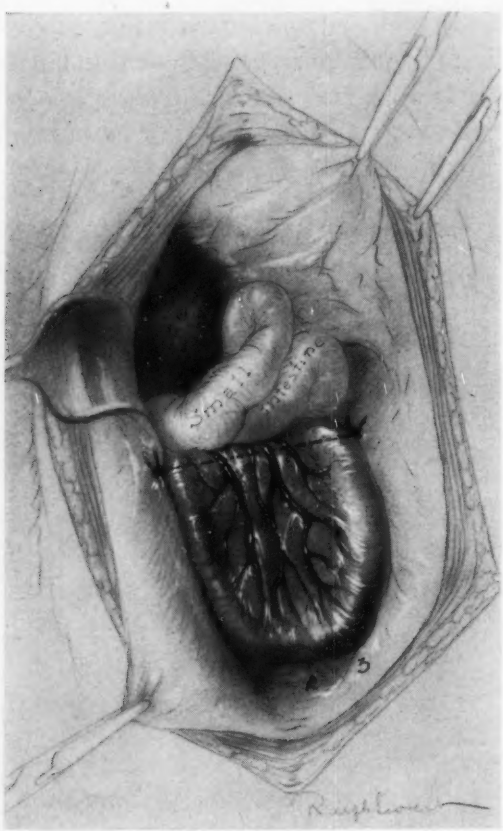

Fig. 8C.

These findings were noted at 6 hours in two of the animals, at 12 hours in three, and at 18 hours in three. Roentgenograms of the other two dogs showed no gaseous distention after 28 hours (Fig. 9). The bowel was gangrenous and autopsy disclosed thrombosis of the involved mesenteric veins. Experiments were not included if gangrenous changes were absent.

DISCUSSION

In order to simulate more closely the findings of strangulating obstruction as seen in our patients, experiments were carried out which brought about a gradual strangulation and obstruction of the lumen of the bowel. Gaseous distention may not occur in experiments such as those cited above which produce occlusion of the mesenteric vessels as in clinical mesenteric thrombosis, particularly of the venous type. Roentgenologic evidences of obstruction were absent in from 20 to 30 per cent

of the animals in which the occlusion was produced in such a manner as to permit intestinal obstruction to occur gradually. This may be explained (1) as a chance finding, although the animals in Group I, which may be considered controls, all had positive x-ray evidence of obstruction; (2) it is possible, however, that mesenteric venous occlusion causes a state of gangrene to occur before the lumen of the bowel is

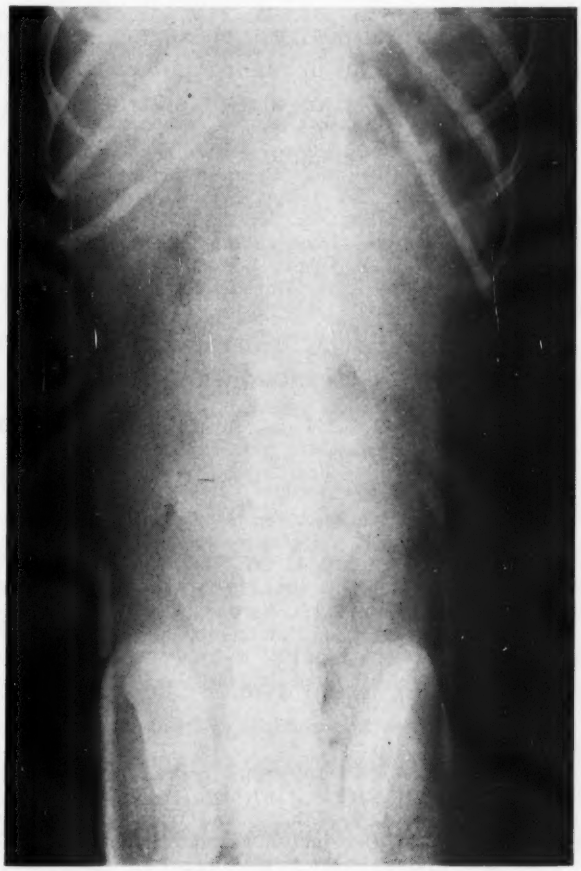

Fig. 9.—Roentgenogram showing absence of gaseous distention in dog in which strangulation obstruction had been produced.

obstructed; (3) this occlusion may provoke a profusion of irritating serosanguineous fluid causing an inhibition of peristalsis and signs of peritonitis so that the x-ray films suggest adynamic ileus or no findings at all; (4) the irritative effect of a band or hernial ring may, by damage to the intima, initiate a venous thrombosis as is produced by simple ligation of a blood vessel.

SUMMARY

1. Two cases of internal strangulating obstruction and gangrenous bowel without x-ray evidence are reported.

2. Strangulating obstruction may be present with x-ray films suggesting adynamic ileus.

3. In ten dogs the sudden production of strangulating obstruction to a loop of small intestine produced x-ray evidence of intestinal obstruction.

4. Gaseous distention was not observed in the roentgenograms of 25 per cent of the twenty dogs in which strangulating obstruction was produced by gradual interference with the blood supply and later with the wall of the bowel itself.

5. Clinical and experimental observations suggest that the absence of evidence of intestinal obstruction in plain roentgenograms may not rule out the likelihood of intestinal strangulating obstruction.

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EXPERIMENTAL STUDIES OF THE VALUE OF SULFATHIAZOLE IN PERITONITIS*

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THE bacteriostatic activity of the sulfonamides has been demonstrated repeatedly both by well-controlled experiments and by the accumulation of clinical observations. The exact mode of action may still be conjecture and a correct understanding of this action may not have been proposed, but the practical observation that these compounds have a highly selective inhibitory effect on the metabolic processes of bacterial reproduction seems well founded. The entire concept of cellular growth and drug action may well be influenced by the studies which have been stimulated in this field.

The use of the sulfonamides locally in the peritoneal cavity has been the natural outgrowth of the first favorable report on the local, bacteriostatic effect by Sinclair and Barker (1937).[1] No attempt will be made to review the past work in this general field. A number of clinical observations have been published on the use of the sulfonamides both by systemic and intraperitoneal administration.[2-6] A lesser number of experimental observations on the local, intraperitoneal use of these substances have been reported.[6-10]

This study is an attempt to determine the relative values of systemic and local intraperitoneal administration of sulfathiazole in treating an experimentally produced peritonitis. In attempting to evaluate the relative effectiveness of a drug it is not necessary to reproduce a specific disease entity, but it is imperative to form a reproducible lesion of sufficient lethal effects to be significant and yet be amenable to treatment to the extent that differential effects to the various forms of treatment being studied can be observed. The preparation of such a test object, an open duodenojejunal loop, as indicated in Fig. 1, seems to fulfill this requirement in that 100 per cent of the control animals died and in that certain forms of therapy protected 100 per cent of the treated animals for a significant period of time.

Experimental Procedure.—After withholding food for twenty-four hours, an upper midline incision was made under ether anesthesia and the duodenum was identified and divided (2 cm.) distal to the main

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pancreatic duct. The jejunum was located and divided distal to Treitz ligament at a point permitting an end-to-end anastomosis to re-establish continuity of the gastrointestinal tract and isolate a segment of bowel approximately 20 cm. long composed of essentially equal lengths of duodenum and jejunum. The proximal end of this segment was closed by inversion (Fig. 1). This isolated loop was washed with 10 c.c. of

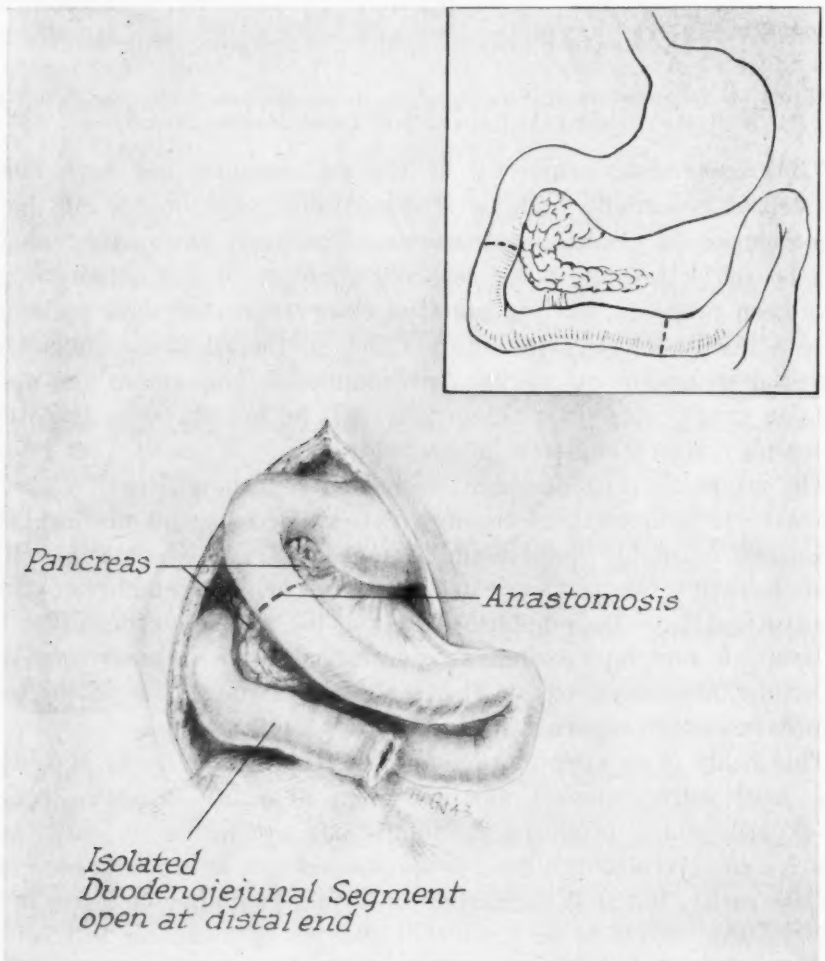

Fig. 1.—Illustrating the operation performed on all of the animals. The duodenum was divided about 2 cm. distal to the pancreatic duct, and the jejunum was divided below Treitz ligament so as to permit an end-to-end anastomosis of the proximal end of duodenum to re-establish continuity with the jejunum. An isolated segment comprised of approximately 10 cm. of each duodenum and jejunum resulted. The duodenal end of this segment was closed by inversion; the distal end was left open to communicate freely with the peritoneal cavity.

physiologically normal sodium chloride solution, and the washings were studied bacteriologically. The loop was dropped into the peritoneal cavity with its distal end open, and the abdomen was closed. This basic procedure was executed in all sixty animals included in this study.

The washings from the loop were exhaustively studied for total bacterial content and for the identification of both aerobic and anaerobic organisms.

Water was always available to the animals, but food was withheld for four days. Practically all of the animals vomited during the first few days following operation. Abdominal distension was seldom present, but muscular rigidity always existed for five to seven days postoperatively when survival occurred.

Ten cubic centimeters of blood were drawn daily for the determination of chlorides, nonprotein nitrogen, plasma protein, hemoglobin, and the concentration of sulfathiazole. These data are summarized in Tables 1,

Table 1 - Group I; control series of animals Duodenojejunal segment washed with 10 cc of physiologically normal salt solution. * See Key to Tables

Animal			D-176	D-177	D-178	D-179	D-180	D-181	D-182	D-183	D-184	D-185
Days of Survival			1½	2½	1½	3½	1	2	1½	3	2	1½
Bacterial Flora	Initial (a)	Count	0	High	High	Low		0	High		Low	High
		Identity	A, P	A,B,C	A,B,G,I	A,B,KM	A,B,D,R	None	A,C,E	A,B,P	A,C	A,B,R,P
	Final (b)	Count	Low	High	High	High	High		High	High	High	High
		Identity	A, P*	A,B,C	A,B,G	A,B,M	A,B,D,R	A,C	A,C,E	A,B,P	A,C	A,B,R,P
Blood Chlorids Mgm %		Initial	399	412	395	392	402	390	398	408	400	406
		Max.	399[1]	412[1]	395[1]	392[1]	402	390	398[1]	408[1]	400[1]	406[1]
		Min.	364[2]	273[3]	334[2]	252[4]	360	330[2]	340	260[3]	345[2]	352[2]
N.P.N. Mgm %		Initial	20.1	34.5	32.7	20.9	25.6	27.4	26.8	24.3	31.3	19.4
		Max.	40.1[2]	128.7[3]	68.4[2]	139.0[4]	32.4	56.2[2]	49.7[2]	96.8[3]	66.7[2]	34.7[2]
		Min.	20.1[1]	34.5[1]	32.7[1]	20.9[1]	25.6	27.4[1]	26.8[1]	24.3[1]	31.3[1]	19.4[1]
Plasma Protein %		Initial	6.35	5.65	6.29	5.70	5.83	6.12	5.92	6.21	5.88	6.05
		Max.	6.35[1]	6.30[2]	6.29[1]	7.66[4]	5.83	6.41	5.92	7.92[3]	5.88[1]	6.26[2]
		Min.	6.17[2]	5.65[1]	5.73[2]	5.35[2]	5.72	6.12[1]	5.71[2]	6.21[1]	5.60[2]	6.05[1]
Hemoglobin Gms/100 cc		Initial	14.30	17.95	22.00	18.80	15.42	19.32	16.84	20.62	21.21	18.93
		Max.	20.55[2]	20.87[2]	25.97[3]	23.60[2]	16.08	24.26[2]	19.74[2]	23.56[1]	23.37[2]	21.42[3]
		Min.	14.30[1]	17.95[1]	22.00[1]	18.80[1]	15.42	19.32[1]	16.84[1]	20.62[1]	21.21[1]	18.93[1]

Key to tables 1, 2, 3, 4, 5, 6

(a) Initial Flora is the bacterial flora present in the segment at the time of operation. (b) Final Flora is the bacterial flora present in the segment and peritoneal cavity at exploration 4 weeks after operation or at autopsy if the animal died sooner than 4 weeks

DESIGNATION OF ORGANISMS: A, Cl welchii; B, B coli; C, alpha streptococcus fecalis; D, beta streptococcus; E, gamma streptococcus; F, Streptococcus liquefaciens; G, Salmonella; H, Staphlococcus albus; I, Staphlococcus aureus; J, B subtilis; K, Diphtheroids; L, B proteus; M, B pyocyaneous; N, Cl sporogenes; P, B aerogenes; Q, B alkaligenes; R, Neisseria flava.

Note: The figures appearing as small superscripts indicate the day of the experiment on which the observation was made. In the bacterial counts "Low" corresponds to a count less than 1000, "Average" 10,000 to 100,000, "High" 1,000,000 or more

2, 3, 4, 5, and 6, respectively, for Groups I, II, III, IV, V, and VI, of ten animals each. Routine autopsies were performed for gross observation and culture of abdominal contents.

Group I.—Ten animals were subjected to the basic operation and served as controls. The average length of survival was two days. Al-

though the survival was brief, the increase of hemoglobin and decrease in blood chlorides reflect the effect of postoperative vomiting resulting from the acute peritonitis which was evident at autopsy, Table 1.

Group II.—Immediately following the operation to form an isolated, open duodenojejunal segment each of ten animals received 0.5 Gm. of sulfathiazole per kilo of body weight, suspended in normal salt solu-

Table 2. Loop washed with 10 cc of physiologically normal salt solution. 0.5 grams of sulfathiazole per kilo of body weight suspended in normal salt solution injected subcutaneously at a single site immediately following operation

Animal		D-132	D-133	D-134	D-135	D-153	D-170	D-171	D-172	D-173	D-174
Days of Survival		3½	2	2	2½	85	4	2	2½	3	20
Bacterial Flora Initial(a)	Count	Low	Average	Low	Average	0	Low	High	Average	Low	0
	Identity	A.B.J.L[4]	A.B.J.L	A.H.K.L	A.B	None	A.B.C	A.B.G	A.B.J.K	A.C.	None
Bacterial Flora Final(b)	Count	High	High	High	High	0	High	High	High	High	Average
	Identity	A.B	A.B.J.L	A.B	A.B	None	A.B.	A.B.G	ABJK	AC	A
Blood Chlorides Mgm	Initial	395	390	409	392	403	404	396	389	406	410
	Max.	395[1]*	390[1]	409[1]	392[1]	403[1]	404[1]	396[1]	389[1]	406[1]	410[1]
	Min.	358[6]	362[2]	394[2]	348[6]	342[3]	310[4]	370[3]	351[2]	321[3]	362[5]
N P N Mgm %	Initial	27.6	30.1	27.6	24.5	25.4	26.2	28.7	25.2	21.3	20.6
	Max.	27.6[1]	30.1[1]	48.6[1]	29.0[1]	35.1[3]	47.6[4]	38.6[2]	36.4[2]	52.1[3]	25.6[2]
	Min.	25.5[3]	27.1[2]	27.6[1]	24.5[1]	25.4[1]	26.2[1]	28.7[1]	25.2[1]	21.3[1]	20.6[1]
Plasma Protein %	Initial	5.75	5.97	5.85	4.93	5.27	5.42	4.96	5.38	5.88	5.78
	Max.	5.75[1]	5.97[1]	5.85[1]	6.58[2]	6.46[1]	6.82[1]	5.36[3]	5.38[1]	6.20[3]	6.10[4]
	Min.	4.88[4]	5.45[2]	4.11[2]	4.93[1]	5.27[1]	5.42[1]	4.96[1]	4.82[2]	5.88[1]	5.20[2]
Hemoglobin Gms/100cc	Initial	21.74	17.47	20.00	15.93	15.73	16.73	18.91	19.26	20.64	18.25
	Max.	22.20[3]	18.68[1]	27.20[3]	19.32[2]	21.90[3]	28.64[4]	23.46[2]	22.82[3]	24.42[3]	19.81[3]
	Min.	20.83[4]	17.47[1]	20.00[1]	15.93[1]	15.73[1]	16.73[1]	18.91[1]	19.26[1]	20.64[1]	13.62[4]
Blood Sulfathiazole Concentration Mgm%	Day 1			0.97		1.08	1.26	1.14	1.32	0.94	1.40
	Day 2	0.43	0.43	1.19	1.29	0.76	1.04	1.00	0.98	1.12	1.31
	Day 3	0.43				1.01	0.76		0.62	0.73	0.79
	Day 4	0.86				0.63	0.43				0.84
	Day 5					0.42					0.53

*See Key to tables

tion, as a subcutaneous injection at a single site. The average survival time was 12.6 days, but it should be observed that this was not an accurate reflection of the true picture, because the increased survival over the control Group I was primarily due to the prolonged survival of two animals, D-153 and D-174 (Table 2) where the initial bacterial flora in the duodenojejunal segment was zero. There is, however, evidence that a small degree of protection has been conferred by this single

subcutaneous dose of sulfathiazole which resulted in but a brief maintenance of a relatively low general systemic concentration of the drug. Twenty per cent of the animals lived more than 15 days. The changes in the composition of the blood were similar to those observed in Group I.

Group III.—One day preceding the usual operative procedures, these ten animals received 2.5 Gm. of sulfathiazole per kilo of body weight, suspended in normal salt solution, by subcutaneous injection at ten different sites. This procedure maintained a significant tissue level of sulfathiazole for approximately 10 days (Fig. 2). From the summarized data in Table 3 it was evident that less vomiting occurred postoperatively. This treatment conferred significant protection with 40 per cent of the animals living more than 15 days and an average survival period of 25.6 days for the entire group. Since the tissue was impregnated with sulfathiazole twenty-four hours before contamination of the peritoneal cavity, this group should represent the best results that can be expected from systemic treatment with sulfathiazole.

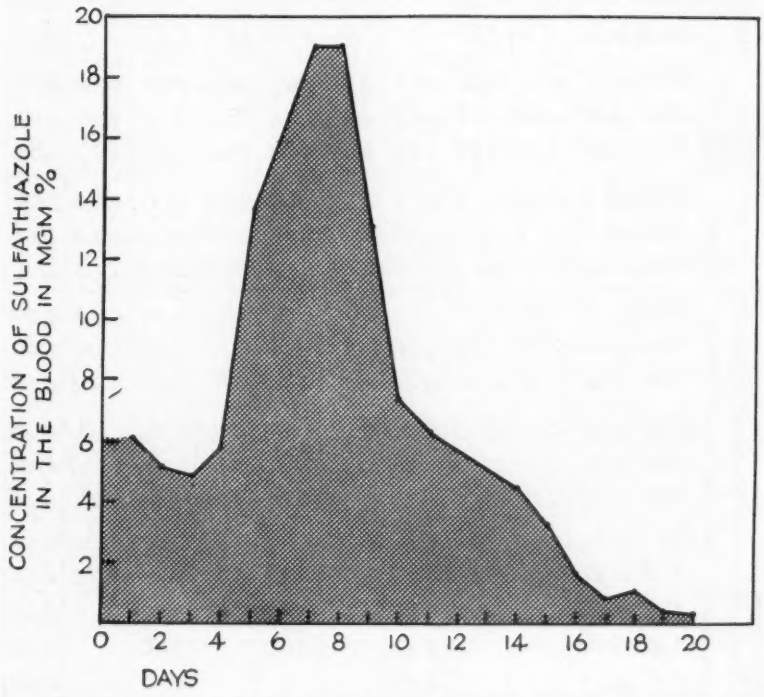

Fig. 2.—A characteristic chart of the concentration of sulfathiazole in the blood following the subcutaneous injection at ten different sites of a saline suspension of 2.5 Gm. of the drug per kilo of body weight.

Group IV.—At the time of the usual operation to form the duodenojejunal segment, 0.5 grams of sulfathiazole per kilo of body weight, suspended in normal salt solution, were injected into the general peritoneal cavity of ten animals. Sixty per cent of these animals survived more than 15 days and the average length of survival was 51.5 days. The concentration of sulfathiazole in the blood was appreciable for

the first 1 or 2 days indicating that the intraperitoneal concentration was high during this period. Those animals which survived more than a few days had only slight changes in the constituents of their blood. At autopsy there was no evidence of "caking" of the drug. The peritoneal cavity contained a moderate amount of clear sanguineous fluid. This fluid did not have a foul odor.

Table 3. Loop washed with 10 cc of physiologically normal salt solution. 2.5 gms of sulfathiazole per kilo of body weight suspended in normal salt solution + divided into 10 portions was injected subcutaneously at 10 different sites 1 day before duodenojejunal loop was made.

Animal		D-147	D-148	D-149	D-150	D-151	D-165	D-166	D-167	D-168	D-169
Days of Survival		70	2	2½	70	1½	4	3	36	2	65
Bacterial Flora	Initial(a) Count	0	Average	0	Average	High	High	Low	Low	0	Average
	Initial(a)	None	A,B	None	C,G	C,G,I,J	A,B,K	A,B,I,J	A,B,C	None	A,B,D
	Final(b) Count	0	High	High		High	High	High	High	High	Low
	Final(b) Identity	None	A,B	A,B		C,G,I	A,B,K	A,B,C,I	A,B,C.	A,C	A,B
Blood Chlorides Mgm.%	Initial	408	400	398	402	411	395	389	406	390	410
	Max.	408*	400	398	402	411	395	389	414	390	418
	Min.	347[4]	316[2]	352	342	386	344	362	392	367	384
N P N Mgm %	Initial	18.4	21.9	32.7	25.5	20.3	19.4	22.6	23.8	18.6	24.3
	Max.	30.6[7]	33.3[2]	32.7	31.8[5]	21.8[2]	34.6	29.8	24.4	26.4	26.8
	Min.	18.4	21.9	24.5[3]	22.0[2]	20.3	19.4	22.6	20.6	18.6	21.3
Plasma Protein %	Initial	5.50	5.10	5.08	5.23	4.65	5.00	4.83	5.20	5.44	4.92
	Max.	5.84[2]	5.20[3]	5.79[3]	5.54[6]	5.34[2]	5.66[6]	5.70[3]	5.55[8]	5.80[2]	5.62[22]
	Min.	5.14[5]	5.10	4.49[3]	4.92[3]	4.65	5.00	4.83	4.96[26]	5.44	4.78[3]
Hemoglobin Gms/100 cc	Initial	19.45	12.52	18.18	18.20	16.40	19.63	14.92	21.64	22.81	17.42
	Max.	19.45	12.52	22.56[3]	20.85[7]	16.40	21.40[3]	18.67[3]	22.04[4]	24.54[2]	19.16[6]
	Min.	12.29[12]	12.12[2]	16.50[3]	18.20	16.17[2]	19.63	14.92	14.36[16]	22.81	11.43[16]
Blood Sulfathiazole Concentration Mgm %	Day 1	4.83	4.50	6.80	10.58	4.38	7.64	5.42	6.21	8.62	5.53
	" 2	8.32	3.91	15.65	5.82	3.67	8.44	4.37	5.48	7.76	8.34
	" 3	10.04		8.96	6.42		9.36	7.73	7.27		9.67
	" 4	12.80			5.19		8.60		9.36		11.32
	" 5	14.13			4.02				10.16		13.61

*See Key to Tables

Group V.—At the time of operation on ten animals, 0.5 Gm. of sulfathiazole per kilo of body weight, suspended in normal salt solution, were injected into the open duodenojejunal loop. A large portion of this fluid naturally poured into the general peritoneal cavity immediately, thereby distributing the drug between the loop and the peritoneal cavity. One hundred per cent of these animals survived for more than 15 days for an average period of 43.1 days. At autopsy these animals

showed a rather dry, chronic peritonitis. The odor was slight. The open end of the duodenojejunal loop was usually walled off, although on occasion it was found entirely free in the peritoneal cavity. It was noteworthy that the blood concentration of sulfathiazole was maintained at a higher level for a longer period than in the case of Group IV.

Table 4. Loop washed with 10cc of physiologically normal salt solution. 0.5 grams of sulfathiazole per kilo of body weight suspended in 20cc of normal salt solution and injected into the general peritoneal cavity as abdomen was closed.

Animal		D-154	D-155	D-156	D-157	D-158	D-186	D-187	D-188	D-189	D-190
Days of Survival		107	137	34	2	2	100	26	3	4	95
Bacterial Flora Initial (a)	Count	Average	Low	Low	Average	Low	0	Average	High	High	Average
	Identity	A.B.N*	ACGH	A.C.R	A.B.K.L	A.1	None	A.B.C	ABCG	ABHR	ABCK
Bacterial Flora Final (b)	Count	Low	Low	High	High	High	0	High	High	High	Low
	Identity	A	A.C	A.B.C	A.B.L	A.B	None	A.C	A.B.C.G	A.B.H	A.B
Blood Chlorides Mgm %	Initial	395	402	392	398	406	399	412	400	408	390
	Max	410^{15}	418^{16}	416^{20}	398^{1}	406	414^{18}	420^{21}	400^{1}	408^{1}	412^{15}
	Min.	376^{4}	402^{1}	382^{3}	374^{2}	361^{2}	381^{3}	366^{4}	356^{3}	342^{4}	370^{3}
N.P.N. Mgm %	Initial	20.6	31.3	24.6	25.4	22.8	23.7	21.5	19.8	17.3	24.8
	Max	27.6^{19}	33.3^{14}	26.4^{8}	35.5^{2}	36.4^{3}	26.5^{11}	24.4^{30}	31.6^{3}	41.6^{4}	26.6^{11}
	Min.	19.4^{3}	27.8^{4}	23.8^{3}	25.4^{1}	22.8^{1}	21.4^{6}	20.7^{8}	19.8^{1}	17.3^{1}	19.4^{27}
Plasma Protein %	Initial	4.35	5.75	5.23	5.97	5.48	5.85	5.10	4.93	5.60	5.27
	Max.	5.10^{16}	6.01^{12}	5.60^{8}	5.97^{1}	5.68^{1}	6.20^{11}	5.72^{8}	5.40^{3}	5.60^{1}	5.92^{30}
	Min.	4.20^{26}	5.65^{21}	5.14^{3}	4.66^{2}	5.48^{1}	5.40^{6}	5.00^{22}	4.93	4.96^{4}	5.11^{4}
Hemoglobin Gms/100cc	Initial	17.48	13.59	15.94	15.90	16.74	18.03	19.24	19.26	18.27	15.47
	Max.	18.35^{3}	15.92^{2}	17.36^{1}	20.40^{3}	19.63^{2}	22.18^{24}	21.18^{14}	21.43^{11}	26.07^{3}	18.18^{18}
	Min.	16.22^{12}	12.18^{9}	13.32^{4}	15.90^{1}	16.74^{1}	16.73^{8}	18.60^{16}	19.26^{1}	18.27^{1}	14.36^{7}
Blood Sulfathiazole Concentration Mgm %	Day 1	4.18	6.24	5.80	5.26	4.78	3.51	4.82	6.21	5.42	3.42
	Day 2	2.06	5.36	6.10	4.18	2.26	3.04	3.67	3.18	4.82	3.26
	Day 3	0.98	1.29	2.42			1.62	1.96		2.76	1.41
	Day 4	0.46	0.76	1.20			0.90	0.53			0.62
	Day 5	0.23	0.31	0.41			0.32	0.71			0.30

*See Key to Tables

Group VI.—In ten animals, 0.5 Gm. of sulfathiazole per kilo of body weight, suspended in normal salt solution, was injected into the open duodenojejunal loop as well as 0.5 Gm. of sulfathiazole per kilo of body weight, suspended in normal salt solution, injected subcutaneously immediately after operation and daily thereafter for 5 days. All of these animals lived longer than 15 days for a survival period of 44.6 days. The blood sulfathiazole was maintained at a significant level for several days although not so high or for as long a period of time as in the case of Group 3. At autopsy a chronic, dry peritonitis was encountered; little odor was present.

DISCUSSION

The results of these experiments to determine the differential advantage of the administration of sulfathiazole by different routes in the treatment of this experimentally produced peritonitis seem quite definite. The experimental preparation employed in this study for the production of a peritonitis caused a 100 per cent mortality for the control animal and was not so severe that it did not respond in a differential manner to the varied forms of therapy used.

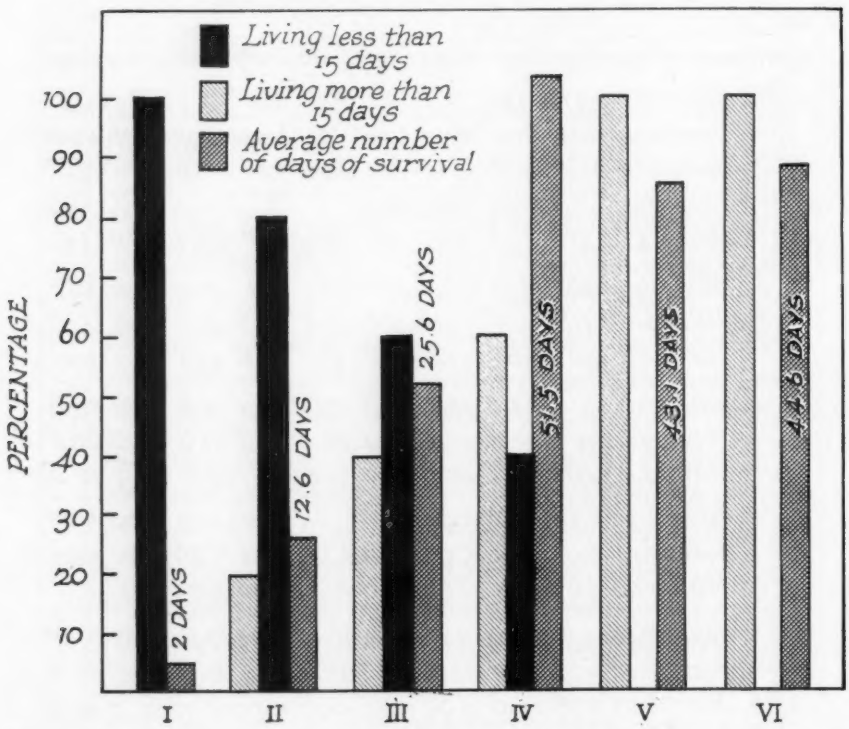

Fig. 3.—Plotting survial data of six groups of ten dogs each, each animal being operated upon to form an isolated, open duodenojejunal segment and treated as follows: Group I: Segment formed but not treated with sulfathiazole. This group of animals to serve as controls. Group II: 0.5 Gm. of sulfathiazole per kilo of body weight injected subcutaneously as a suspension at a single site immediately following operation. Group III: 2.5 Gm. of sulfathiazole per kilo of body weight injected subcutaneously as a suspension in ten different sites on day preceding operation. Group IV: 0.5 Gm. of sulfathiazole per kilo of body weight injected into the peritoneal cavity as a suspension at time of operation. Group V: 0.5 Gm. of sulfathiazole per kilo of body weight injected into the open duodenojejunal segment as a suspension at time of operation. Group VI: 0.5 Gm. of sulfathiazole per kilo of body weight injected into the open duodenojejunal segment and an equal quantity of the drug injected subcutaneously as a suspension in a single site at time of operation and for 4 successive days thereafter.

The data obtained in these experiments have been summarized in the tables and are included because of the wide difference between the bacterial flora present in individual animals and these facts make it imperative that exact information be available in an experiment including such small numbers of animals. Reference to the tables will show that the bacterial flora in the duodenum and first part of the jejunum may not be small, as is frequently assumed. The number of organisms may be as

great as are encountered in the large bowel, therefore, to draw any conclusions from an individual experiment, this information is essential and must be recorded.

The duodenojejunal loop, open at one end, serves as a constant source of infection. The deposition of sulfathiazole into this loop serves a double purpose. The drug alters and probably attenuates the contained bacterial flora and acts as a reservoir of drug which is subsequently

Table 5 - Loop washed with 10cc of physiologically normal salt solution. 0.5 grams of sulfathiazole per kilo of body weight suspended in 20 cc of normal salt solution injected into the open duodenojejunal loop.

Animal			D-141	D-142	D-143	D-144	D-145	D-160	D-161	D-162	D-163	D-164
Days of Survival			35	68	50	30	45	75	26	32	47	53
Bacterial Flora	Initial(a)	Count	Average	0	Low	High	High	Low	High	High	Low	Average
		Identity	A.B D.J.R *	None	C.E	B.L	A B H K M R	A.C.E	A B J L	A B D R	A B C	A E L
	Final(b)	Count	Average		Average	High	High	Low	High	High	Average	High
		Identity	C.D		A.C.J.K	A.B.C.I	A.B.C	H	A B C	A.B	A.B.C	A.L
Blood Chlorides Mgm.%		Initial	403	400	407	392	396	405	420	380	410	396
		Max.	406[15]	411[6]	411[7]	410[14]	403[14]	416[12]	442[16]	396[17]	422[13]	406[8]
		Min	356[2]	379[2]	378[3]	299[4]	329[5]	390[4]	330[3]	321[5]	376[5]	385
N.P.N Mgm.%		Initial	20.0	21.1	27.7	25.2	29.3	26.1	24.5	22.6	23.4	26.8
		Max.	25.9[16]	29.7[15]	27.7[1]	33.1[14]	29.3[1]	28.9[13]	30.6[14]	31.6[15]	27.5[10]	28.7[8]
		Min.	18.5[10]	20.5[3]	22.3[1]	17.7[2]	17.5[7]	22.7[5]	18.6[11]	17.3[4]	20.1[2]	22.4[3]
Plasma Protein		Initial	4.35	5.23	5.48	5.10	5.60	4.80	5.32	4.68	5.52	4.76
		Max.	5.20[22]	5.24[15]	5.54[9]	5.55[3]	6.51[3]	5.20[8]	5.70[3]	5.62[14]	5.71[17]	4.92[3]
		Min.	3.89[8]	4.23[3]	4.77[15]	4.71[2]	4.29[7]	4.52[9]	4.30[8]	4.28[3]	5.21[8]	4.36[7]
Hemoglobin Gms./100 cc		Initial	13.95	17.68	15.09	17.23	18.30	16.87	19.62	14.63	15.74	20.46
		Max.	18.40[3]	20.40[23]	15.58[2]	17.70[14]	21.60[3]	17.23[11]	22.34[4]	18.76[12]	16.36[19]	22.16[5]
		Min.	10.22[6]	12.51[15]	10.02[8]	15.85[5]	10.30[15]	12.60[30]	10.16[18]	12.42[26]	14.71[24]	19.87[19]
Blood Sulfathiazole Concentration Mgm.%		Day 1	6.42	3.79	6.42	1.29	3.21	5.31	4.32	5.80	3.92	6.20
		" 2	7.93	2.53	5.94	2.64	2.18	5.11	3.26	3.92	4.10	5.50
		" 3	0.86	1.51	2.30	4.14	3.09	3.26	2.72	2.14	2.05	3.64
		" 4	0.86	0.43	2.18	1.73	1.73	1.60	1.40	1.70	1.64	2.82
		" 5	0.54	1.29	1.73	1.40	2.64	1.10	0.92	1.02	0.52	1.31

*See Key to Tables

forced into the general peritoneal cavity to replace the drug absorbed by the peritoneal surfaces as indicated by the relative blood levels of sulfathiazole in Groups IV and V.

The survival of the animals in Groups IV, V, and VI, and especially in Groups V and VI, as contrasted with the survival rates in Groups II and III, demonstrated the importance of, and the therapeutic value of, main-

taining a high local concentration of sulfathiazole in the area of infection. These observations logically suggest a possible value of repeated injections of a suspension of sulfathiazole into the peritoneal cavity in the presence of a generalized peritonitis, without localization, to maintain a sustained high local concentration of the drug over an extended period.

Table 6.—Loop washed with 10 cc of physiologically normal salt solution 0.5 grams of sulfathiazole per kilo of body weight suspended in 20 cc of 7% injected into the open duodenojejunal loop 0.5 gms. of sulfathiazole per kilo of body weight suspended in 20 cc of 7% deposited.

Animal			D-120	D-122	D-124	D-125	D-126	D-127	D-129	D-130	D-137	D-139
Days of Survival			60	22	16	60	17	71	50	50	40	60
Bacterial Flora	Initial (a)	Count	Low	High	High	Low	Low	Average	Average	Low	High	Average
		Identity	A.H I.K.R	A.B.P	A.I.M	N	A.B.C	A.B.H.I K.L.Q	A.B.G	A.B.C	A.B.N	A.M
	Final (b)	Count	High	High	High	Low	High	Low	Average	High	High	High
		Identity	A.C.P	A.B.P	AM	ACH	ABCL	AHKQ	CH	A.G	BF	C
Blood Chlorides Mgm %		Initial	405	394	392	398	416	404	395	402	405	407
		Max.	419[10]	413[16]	392[1]	436[20]	416[1]	436[16]	409[16]	421[28]	430[15]	423[11]
		Min.	354[2]	322[3]	220[15]	300[5]	356[5]	324[4]	271[27]	300[6]	328[3]	377[5]
N.P.N Mgm %		Initial	23.7	27.5	25.5	24.0	26.1	29.8	19.3	19.3	25.4	24.7
		Max	39.5[5]	30.6[5]	42.1[15]	39.6[5]	27.1[8]	66.2[4]	71.3[27]	29.4[31]	29.4[5]	37.2[24]
		Min	18.7[43]	17.1[19]	21.7[18]	22.3[47]	22.7[3]	20.3[31]	18.4[2]	19.3[1]	15.1[2]	18.7[2]
Plasma Protein %		Initial	5.84	6.26	4.95	6.27	6.41	5.31	5.09	6.59	6.29	4.85
		Max	6.20[20]	7.20[3]	5.29[2]	7.10[33]	6.41[1]	6.01[4]	6.33[23]	7.14[31]	6.29[1]	5.55[18]
		Min.	4.64[8]	5.43[18]	4.23[13]	4.30[14]	4.67[5]	4.54[16]	4.52[6]	5.30[22]	4.86[15]	4.41[10]
Hemoglobin Gms./100 cc		Initial	16.52	15.92	20.17	18.30	18.42	14.65	15.03	12.79	19.18	15.92
		Max.	22.02[2]	21.60[6]	22.65[2]	20.84[2]	19.89[2]	15.84[2]	15.83[27]	16.83[2]	21.58[4]	17.60[2]
		Min.	11.39[12]	8.76[21]	17.2[13]	8.11[20]	10.71[8]	5.46[17]	8.58[6]	6.65[28]	12.10[29]	7.97[10]
Blood Sulfathiazole Concentration Mgm %		Day 1	11.08	3.91	4.26	6.42	5.31	3.44	2.64	4.02	2.75	5.07
		" 2	9.37	3.55	2.64	5.07	6.67	3.97	3.55	2.41	4.61	2.18
		" 3	1.95	2.64	2.86	3.09	1.73	2.21	2.30	2.86	7.30	1.62
		" 4	1.29	2.18	1.51	1.73	1.84	2.96	0.86	1.73	3.09	5.44
		" 5	2.53	4.02	1.95	1.73	1.29	1.08	1.73	1.29	3.09	1.40

*See Key to Tables

Groups V and VI cannot be compared directly with the preceding groups because the drug had been placed in the loop and probably served to attenuate the organisms, inhibit their growth, or prevent the formation of greater quantities of sulfonamide inhibitors by the metabolic action of the bacteria in the loop, so that these elements contaminated the general abdominal cavity to a lesser degree.[11] These ex-

periments should serve, however, to demonstrate the beneficial effect of a high local concentration of the drug in controlling infection.

While Groups V and VI fail to show any difference in the effectiveness of treatment because 100 per cent survival resulted in both experiments, Stafford (1942),[12] in contrasting two series of acute appendicitis with peritonitis and abscesses, showed that the incidence of secondary complications were decreased following the use of sulfathiazole by mouth or intravenously. From these observations it would appear that the sulfonamides should be given by both the intraperitoneal and other routes to establish a high local concentration and maintain the desired systemic drug level in the treatment of peritonitis.

A suspension of sulfathiazole in contradistinction to the dry powdered form of the drug is apparently more uniformly distributed and shows little tendency to "cake" or act as an irritating foreign body and may permit the use of this more powerful bacteriostatic agent instead of the more toxic and less active sulfanilamide, which has been favored for intraperitoneal insufflation because of its more suitable physical properties.

The value of using sulfathiazole locally in the peritoneal cavity in conjunction with succinylsulfathiazole, when employed to alter the bacterial flora of the intestinal tract[13-16] prior to elective surgery on the large bowel, becomes evident and is advocated as an additional adjuvant to modern surgery of the colon whenever soiling occurs during operation.

SUMMARY

1. A method for maintaining a therapeutic concentration of sulfathiazole in experimental animals over a long period is described.

2. A simple preparation for the production of a generalized peritonitis well suited to the study of the value of chemotherapeutic agents is presented.

3. A study of the bacterial flora of the duodenum and upper jejunum is reported.

4. The value of sulfathiazole when applied locally to the peritoneal cavity is assessed as compared to its usefulness when administered so as to maintain a relatively high general tissue concentration.

5. The suggestions are made that a suspension of sulfathiazole may be more suitable than the dry powder for intraperitoneal administration and that repeated intraperitoneal injections may be advisable in generalized peritonitis.

6. The results of this study indicate that the intraperitoneal administration of sulfathiazole should be fortified by maintaining a high systemic concentration of the drug by other therapeutic routes when necessary.

7. The combined use of succinylsulfathiazole and sulfathiazole as an adjuvant to surgery of the large bowel is advocated.

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ANOXIA AND ANESTHESIA IN INTRATHORACIC OPERATIONS

A Clinical Study*

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ANOXIA, a diminution in the normal amount of oxygen in the various tissues and organs of the body, was the most important single factor which delayed the development of surgical operations for lesions within the thoracic cavity. Since the heart and lungs are chiefly responsible for supplying oxygen to the tissues, alteration of their function by opening the chest led to serious consequences. The ill effects of an open pneumothorax on cardiorespiratory function were demonstrated as long ago as the sixteenth century by the anatomist Vesalius[1] to his students. He also demonstrated to them, by the use of a reed in the trachea, how these deleterious reactions could be prevented or overcome by repeated inflation of the lung. Before the establishment of aseptic surgical principles by Lister[2] and the development of diagnostic methods (Roentgen,[3] and Killian[4]), the experimental findings of Vesalius could not be applied in clinical practice until within the last two or three decades.

The importance of anoxia occurring during surgical procedures in general has recently received more attention (McClure and associates,[5] and Schnedorf and associates[6]). The chief investigation has been directed toward the anesthetic agent used and the amount of available oxygen during the operative procedure.

The anesthetic agent of choice and the method of administration for intrathoracic operations continue to be controversial problems. Some anesthetists or surgeons prefer cyclopropane,[7, 8] while others prefer ether,[9] ethylene,[10] or spinal anesthesia.[11] Opinions are also divided as to whether an intratracheal catheter is advisable and, if so, in what types of patients or diagnostic conditions.[7, 9, 12-15] Most surgeons at the present time are agreed that the anesthetic mixture should be administered under mild positive pressure when the pleural cavity is opened.

Since alteration of cardiorespiratory function is apt to occur when the pleural cavity is opened, the role of anoxia assumes even greater importance in intrathoracic operations.

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CONTRIBUTORY FACTORS IN THE PRODUCTION OF ANOXIA IN INTRATHORACIC OPERATIONS

In the transportation of oxygen from an inhaled gas to various tissues of the body, certain factors especially related to intrathoracic operations may play a major part in the development of anoxia (see Table I).

When the pleural cavity is opened there is an immediate reduction of negative pressure on the opposite side. With each inspiratory effort the mediastinum is pulled toward the unoperated side, thus further reducing the effectiveness of the respiratory effort. The hindrance of action of the respiratory muscles may be considerable, due to the use of self-retaining rib spreading retractors and the side position with slight Trendelenburg on the operating table, particularly in older, obese, or debilitated patients. Thus, it is obvious that decreased efficiency of the respiratory effort can materially reduce the amount of gas exchange within the lungs and lead to the development of anoxia.

Ventilation of the lung may be further decreased by obstruction of the air passages with mucus, pus, or blood. This is more likely to occur in patients with suppurative diseases of the lung. The vital capacity may be already considerably reduced due to inflammatory, neoplastic, or degenerative changes in the lung, and will be further reduced by collapse of the lung when the pleura is opened.

It is a well-known fact that the respiratory reserve of a normal man or animal is high, several times the amount of function ordinarily needed (Graham,[16] Phillips and co-workers,[17] and Rasmussen and co-workers[18]). It has also been repeatedly demonstrated that operations in the open thorax may be made under spinal anesthesia with little or no positive pressure applied to the tracheobronchial tree (Edwards,[11] and Magill[19]). However, since many patients needing intrathoracic operations already have a reduction in the respiratory reserve, most surgeons have agreed that a mild increase in the intrabronchial pressure is advisable during these procedures. This pressure should not be so high as to obstruct the flow of blood through the lungs, thus producing decreased cardiac output with a resultant drop in systemic blood pressure, but only enough (4 to 8 mm. Hg) to stabilize the mediastinum and keep the lungs partly inflated.

Obstruction of the air passages may be obviated by preoperative removal of secretions and pus by postural or bronchoscopic drainage. During operation, a slight lowering of the head of the table (20 to 30 degrees) will aid in the removal of mucus and pus by gravity drainage. In patients having a productive cough, bronchoscopic aspiration in the operating room following surgery is the routine in this clinic. In cases of bilateral bronchiectasis, Blades and Graham[20] have advocated elevation of the head of the table during operation to aid in "internal drainage" of secretions from the lobes to be removed into the lower lobe

TABLE I

CONTRIBUTORY FACTORS IN THE PRODUCTION OF ANOXIA DURING INTRATHORACIC OPERATIONS

DECREASED EFFICIENCY OF THE RESPIRATORY EFFORT
Open chest
1. Loss of negative intrapleural pressure
2. Movement of mediastinum
3. Inefficient muscular activity
Position on table
1. Interferes with chest motion
2. Good lung dependent
Diaphragmatic paralysis
DECREASED VENTILATION OF LUNG
Obstruction of airway by secretions
Collapse of lung
Removal of lung
Disease of lung
1. Inflammatory
2. Neoplastic
3. Emphysema—asthma
4. Fibrosis
DECREASED CARDIAC OUTPUT
Obstruction of veins and auricles by retractors and lap pads
Increased intrabronchial pressure
Abnormal cardiac action
1. Tachycardia
2. Flutter
3. Fibrillation
ALTERATION OF O_2 TRANSPORT MEDIA
Anemia
Blood loss during and following operation
Arteriovenous shunt (collapsed lung)

of the dependent side. Following the operation the air passages are thoroughly cleared by bronchoscopic aspiration.

Attention must be given to the careful use of large, moist gauze packs and retractors since little pressure is needed to obstruct the blood flow through large veins, or to compress the auricles, thus leading to decreased cardiac output and lowering of systemic blood pressure.

Many patients requiring operations within the chest have some degree of anemia when first seen. Since normal cardiac action and sufficient respiratory reserve with adequate gas exchange in the lungs will not compensate for lack of hemoglobin, treatment of this anemia with blood transfusion is indicated. In addition to the administration of blood before surgery, a continuous transfusion of 500 to 1,000 c.c. (or at times more) during operation is almost routine at our clinic. This is usually no more than replacement of blood lost during and immediately following the operation and goes far in the prevention of anoxia as well as shortening convalescence. This blood is given before any evidence of shock appears.

In a previously reported series of intrathoracic operations,[10] no blood transfusions were given in the operating room and no symptoms of shock were observed. However, postoperative hematocrit studies re-

vealed that a moderate to severe grade of anemia was present without evidence of circulatory failure.

Since the reduction in arterial blood oxygen may have a severe detrimental effect on the patient both during and following the operation, we have thought it worth while to investigate its frequency and severity in our patients. The continual controversy regarding both the most desirable anesthetic agent and the proper method of its administration in intrathoracic operations has been an added stimulus for this inquiry. To this end both clinical and experimental studies have been conducted. A preliminary report of the clinical work appears elsewhere,[21] and a complete report of the experimental investigation will be published in a separate communication.[22]

In order to determine the maximum influence of the operative procedure as well as the anesthesia on arterial blood oxygen, specimens of arterial blood were taken near the end of the operation just before closing the pleural cavity. These were obtained from the radial or brachial artery using a mercury tenonometer. This sample was then compared with samples of arterial blood obtained during the twenty-four hours prior to operation, and again four to fourteen days following operation. Erythrocyte count, hematocrit, hemoglobin, and oxygen content determinations were made on these specimens of arterial blood. The oxygen content was determined according to the Van Slyke-Neill[23] manometric method and the value recorded in volume per cent. The anesthetic record of each patient showed the per cent of oxygen in the anesthetic mixture when the sample of arterial blood was obtained as well as the average percentage of oxygen used during the entire operation. This was then compared to the oxygen in the three samples of arterial blood. All blood oxygen determinations were made in duplicate.

In the preparation of our patients for intrathoracic operations, attention has been given to blood transfusion in patients with anemia, and to postural or bronchoscopic drainage in patients with suppurative disease of the lung. In patients with esophageal obstruction due to carcinoma of the esophagus or cardia, water and electrolyte losses are replaced and the nutritional state improved before undertaking the operative procedure. During this study most of our patients received morphine (0.010 to 0.015 Gm. [hypodermic]) and calcium nembutal (0.18 to 0.27 Gm. in 50 c.c. of water per rectum) one and one-half hours before anesthesia. The dosage varied according to the age, size, sex, and general condition of the patient. In patients with hypertension, avertin (approximately 70 to 80 mg./kilogram) was sometimes employed for basal anesthesia, particularly when N_2O-O_2 anesthesia was to be used because of the presence of electrical devices.

The anesthetic mixture used for these operations for the most part was ethylene plus oxygen or ethylene-oxygen plus ether. The anesthetic mixture depended upon the degree of resistance of the patient and the

need for deep anesthesia. At one time ethylene plus oxygen alone was used and the percentage of ethylene was increased when deeper anesthesia was needed. It was found, however, that in patients with pulmonary suppurative disease this was at times unsatisfactory because of symptoms of anoxia and we have since added ether and more oxygen, thereby obtaining deeper anesthesia and better oxygenation. During the closure of the chest wall in this latter group of cases, nitrous oxide-oxygen is substituted and explosive mixtures in machines are removed from the room. This permits the use of bronchoscopic aspiration for the thorough clearing of the air passages of pus and secretions at the end of operation.

The anesthetic agent in this series of operations has been administered under slight positive pressure (4 to 8 mm. Hg) using the semiopen system with a snug-fitting face mask. An intratracheal catheter has only occasionally been employed and this was in patients with bilateral bronchiectasis who were raising a large amount of sputum. It has not

TABLE II

DIAGNOSIS, NUMBER AND CAUSE OF POSTOPERATIVE DEATHS OCCURRING IN 51 INTRATHORACIC OPERATIONS (45 PATIENTS)

DIAGNOSIS	NO. OF PATIENTS	NO. OF DEATHS	TIME OF DEATH	CAUSE OF DEATH
Carcinoma of lung	9	1 exploratory thoracotomy	3 days P.O.	Pulmonary edema
		2 pneumonectomy	2 weeks P.O.	Anuria
			2 weeks P.O.	Pericarditis
Bronchiectasis	10*	1 bilobectomy (bilateral bronchiectasis)	4 days P.O.	Pneumonia
Carcinoma of esophagus or stomach (Benign stricture, 1)	12	2 carcinoma of cardia resection	8 days P.O.	Massive empyema
			1 day P.O.	Cardiac failure
Mediastinal tumor or cyst	3	None	-	-
Malignant hypertension (14 operations)	8	None	-	-
Constrictive pericarditis	2	None	-	-
Patent ductus arteriosis	1	None	-	-

*One case of infected cyst of the lung and one of chronic infection of the lung are included in this group.

been found necessary in other patients, and the elimination of irritation of the tracheal mucous membrane from the presence of a foreign object for a period of time, we feel, has definitely improved the convalescence period. At the termination of the operation, complete obliteration of the pleural space through re-expansion of the lung was obtained by aspiration of the residual air through a pezzer catheter drain rather than by distention of the lung through the use of a high intrabronchial pressure. This prevents the driving of infectious material out into the periphery of the lung as well as overdistention and damage of the lung

tissue. The pathologic lesions included in this study as well as the postoperative deaths are presented in Table II. A variety of operations were made on these patients, as shown in Table III.

TABLE III

TYPE OF OPERATION

	NUMBER	DEATHS
1. Exploratory thoracotomy for:		
Carcinoma of lung	6	1
Carcinoma of esophagus or cardia	6	0
2. Pneumonectomy	3	2
3. Lobectomy or bilobectomy	10	1
4. Extirpation of mediastinal tumor or cyst	3	0
5. Partial resection of thoracic esophagus or esophagus and stomach	6	2
6. Thoracic paravertebral sympathectomy	14	0
7. Pericardectomy (partial)	2	0
8. Ligation of patent ductus arteriosis with associated subacute bacterial endarteritis	1	0

None of the deaths in this group were related directly or indirectly to the anesthesia. One postpneumonectomy death was due to anuria following the administration of sulfathiazole in the usual amount. The death following exploration for carcinoma of the lung was due to cardiac failure. The operation should not have been made since the arterial blood oxygen was only 11.64 volumes per cent before operation. One child with bilateral bronchiectasis died of pneumonia four days following a bilobectomy. This was believed to be due to the poor general condition and massive and prolonged lung disease. Cardiac failure was responsible for one death twenty-four hours following an esophageal resection for carcinoma, while a second death was due to leakage of the anastomosis with massive empyema following the resection of 80 per cent of the stomach and lower esophagus. Most of these deaths occurred in poor-risk patients.

RESULTS

The results are presented in Tables IV, V, VI, VII, and VIII. The data are arranged to show values of arterial blood samples obtained before, during, and following the operative procedure and are grouped according to the anesthetic agents employed. The anesthetic risks are given in the second column, i.e., E, excellent; G, good; F, fair, and P, poor. This risk was determined on the basis of the patient's general condition, degree of toxicity, and debilitation, in addition to the local disease.

Thoracic Sympathectomy for Essential Hypertension (Table IV).—Fourteen operations made on eight patients are included in this group. Although the majority of these patients were considered only fair or poor operative risks, judged by cardiorenal and vascular changes, there was no operative mortality. Each operation consisted of two transpleural approaches (through the third and tenth rib-beds) for removal

of the entire thoracic sympathetic chain and usually included the first lumbar ganglion. The operating time for this group averaged two hours.

With the exception of patients Nos. 2, 5, and 6 the condition of the preoperative blood was within normal limits. In Nos. 5 and 6 the hypertension was so great that a transfusion for correcting a marked anemia was thought to be hazardous.

Throughout this group the state of the arterial sample taken at operation showed little change from that of the preoperative specimen. The oxygen values of some patients were higher during operation, while others were slightly better before operation. The postoperative samples will be discussed later. With the exception of patients Nos. 4, 5, and 6 no anoxia was observed; however, Nos. 5 and 6 were actually improved in comparison to their preoperative state. In spite of the degree of anoxia present in this patient (A. P.) no cyanosis was observed because of the degree of anemia present.

The percentage of oxygen used in the anesthetic mixtures varied from 12 to 40. Equally satisfactory blood oxygenation was obtained with the four different anesthetic mixtures used.

Carcinoma of the Esophagus or Cardia (Table V).—Of the twelve operations in this group, six were resections and six were only explorations. Due to the nature of the condition all operations lasted at least two hours and some resections required four hours. The majority of these patients required opening of the diaphragm in addition to the thoracotomy wound; and in some either a gastrostomy, gastroesophagostomy, or a cervical esophagostomy was made. As a group they were considered a better operative risk than those in Table IV, most patients being classified as good or fair. There were no anesthetic deaths. With the exception of the first patient the preoperative blood samples showed relatively normal values and remained the same during the operation. Ten of the twelve operations were made under an anesthetic mixture of ethylene plus 13 to 48 per cent oxygen. The preanesthetic medication produced marked depression in patient No. 10, thus demanding a higher percentage of oxygen in the anesthetic mixture. No cyanosis was observed in this group of patients and blood oxygenation was satisfactory. The postoperative values were often lower than the preoperative and operative levels and will be discussed later.

Carcinoma of the Lung (Table VI).—Nine patients are included in this group, in four of whom only an exploratory thoracotomy was made. This group as a whole were fair-risk patients, with the exception of patients Nos. 2 and 4. The operations lasted for an average of two and one-half hours. In patients Nos. 1, 2, 6, and 9 an exploration only was made. However, before operability could be determined, a considerable amount of dissection was necessary in both patients Nos. 2 and 9.

In patient No. 2 exploration was probably inadvisable due to his extremely poor condition. Cyanosis was not present either before or

TABLE IV

STATE OF ARTERIAL BLOOD BEFORE, DURING, AND FOLLOWING TRANSPLEURAL THORACIC SYMPATHECTOMY IN 8 PATIENTS (14 OPERATIONS)

PATIENT	PREOPERATIVE						DURING OPERATION						POSTOPERATIVE			
	CONDITION	HB. (%)	R.B.C.	HMCRT.	BLOOD O_2	O.T. HR.	HB. (%)	R B.C.	HMCRT.	BLOOD O_2	O_2 GIVEN A	O_2 GIVEN B	HB. (%)	R.B.C.	HMCRT.	BLOOD O_2
Ethylene + O_2 Anesthesia																
1. P. L.	P	92	4.46	38	16.44	2¼	90	4.4	36	13.95	14	15	70	4.6	30	12.52
2. P. L.	P	80	5.05	34	13.37	1½	82	5.0	35	14.67	15	18	80	4.0	35	15.23
3. J. L.	G	100	5.1	35	18.82	1¾	96	4.9	34.5	18.96	20	20	102	5.0	35	17.79
4. D. M.	F	96	4.0	32	14.92	1¾	102	4.4	33	12.11	15	16	82	4.1	31	15.14
5. A. P.	P	70	4.2	27	10.91	2	74	4.3	30	11.26	15	15	60	3.8	28.5	10.65
6. A. P.	P	60	3.8	28.5	10.65	2	68	4.0	32	11.88 During transfusion	15	15	68	4.1	31	11.92
Ethylene + O_2 + Ether Anesthesia																
7. V. M.	F	105	5.5	41	19.92	2½	106	5.4	43	21.41	25	31	104	5.25	39	18.39
8. J. M.	F	92	4.8	36	16.90	2¼	90	4.7	36	17.00	28	25	80	4.4	33	13.10
9. C. C.	G	110	6.17	45	19.41	2¼	112	6.0	43	19.63	18	25	90	5.1	42	18.42
10. C. C.	G	90	5.1	42	18.42	2	90	5.0	40	17.33	18	24	90	4.8	40	16.91
Ethylene + O_2 + Avertin Anesthesia																
11. H. M.	F	100	4.6	39	19.06	2¼	106	4.8	43	20.50	12	13	92	4.5	38	19.11
12. H. M.	F	92	4.5	38	19.11	2	102	4.7	30	16.04	25	27	104	4.9	39	17.64
13. V. M.	F	104	5.25	39	18.39	2	110	5.3	39	16.93	25	35	108	5.2	35.5	13.70
Ethylene + O_2 + Vinethene Anesthesia																
14. D. M.	F	100	4.5	35.5	14.57	2¼	98	4.4	35	16.97	30	40	96	4.0	32	14.92

During the operation, arterial blood was obtained just before closure of the pleural cavity. The condition of the patient is given as G-good, F-fair, or P-poor. Abbreviations: Hb., hemoglobin; R.B.C., red blood cells; Hmcrt., hematocrit; O_2, oxygen; O.T., operating time in hours; oxygen given, A—average per cent during the entire operation, B—per cent of oxygen being given when arterial blood sample was obtained.

TABLE V

STATE OF ARTERIAL BLOOD BEFORE, DURING, AND FOLLOWING TRANSPLEURAL OPERATION FOR CARCINOMA OF THE ESOPHAGUS OR CARDIA IN 12 PATIENTS

PATIENT	PREOPERATIVE						DURING OPERATION						POSTOPERATIVE			
	CONDITION	HB. (%)	R.B.C.	HMCRT.	BLOOD O_2	O.T. (HR.)	HB. (%)	R.B.C.	HMCRT.	BLOOD O_2	O_2 GIVEN A	O_2 GIVEN B	HB. (%)	R.B.C.	HMCRT.	BLOOD O_2
Ethylene + O_2 Anesthesia																
1. A. M.	P	76	4.05	34	12.57	3¾	80	4.26	35	13.81	15	15	70	4.21	35.5	14.03
2. M. W.*	G	86	5.0	35	16.44	2	84	4.9	37	15.54	17	16	84	4.6	35	14.88
3. N. D.*	G	88	4.8	34	18.23	2½	84	4.7	35	16.37	16	16	100	4.1	35	18.86
4. S. C.*	G	90	4.8	40	19.40	2¼	94	4.7	40	17.35	15	15	80	4.4	32	14.62
5. B. H.	G	116	5.0	46.5	20.98	2	114	4.7	47	20.81	15	15	82	4.5	32	15.35
6. S. S.	E	94	5.5	34	17.53	4	92	5.3	36	17.94	20	20	78	3.6	30	14.32
7. J. T.*	G	92	4.2	34.5	17.45	3	98	4.4	35.5	18.09	20	20	92	4.2	33	15.52
8. H. L.*	F	94	4.28	37	18.53	2	92	4.1	38	18.90	25	35	84	4.2	35	17.38
9. C. P.*	F	100	4.95	40	18.01	2¼	102	4.9	40.5	17.98	13	13	94	4.5	38	14.48
10. P. V.	P	98	4.4	38	16.78	2½	94	4.5	37	17.04	42	48	78	4.0	34	14.44
Ethylene + O_2 + Ether Anesthesia																
11. D. G.	F	100	4.9	45	16.81	3¾	78	4.95	45	18.45	15	15				
12. P. A.	F	114	5.2	42	19.17	4¼	110	5.1	41	21.52	37	40	100	5.15	32	13.69

*Exploratory thoracotomy only.

See Table IV for explanation of abbreviations.

TABLE VI

CONDITION OF THE ARTERIAL BLOOD BEFORE, DURING, AND FOLLOWING A TRANSPLEURAL OPERATION FOR CARCINOMA OF THE LUNG

PATIENT	PREOPERATIVE						DURING OPERATION						POSTOPERATIVE			
	CONDITION	HB. (%)	R.B.C.	HMCRT.	BLOOD O_2	O.T. (HR.)	HB. (%)	R.B.C.	HMCRT.	BLOOD O_2	O_2 GIVEN A	O_2 GIVEN B	HB. (%)	R.B.C.	HMCRT.	BLOOD O_2
Ethylene + O_2 Anesthesia																
1. S. S.*	G	94	4.2	38.5	16.75	2	92	4.1	34	17.01	20	24	94	5.1	34	17.54
2. M. L.*	P	90	4.8	32	11.64	2¼	88	4.8	31	11.10	40	40				
3. W. E.	F	70	4.5	40	16.15	2¼	76	4.98	45	18.47	15	20				
4. F. F.	P	74	4.3	40	14.18	3	65	4.1	37	11.72	22	35				
Ethylene + O_2 + Ether Anesthesia																
5. R. T.	G	100	4.8	32	15.83	2¾	105	4.8	38	12.83	41	45	110	5.2	42	14.35
6. E. B.*	F	105	5.1	56	16.85	1½	108	5.3	58	18.18	25	28	100	4.4	52	17.56
7. J. K.	F	102	4.5	35	16.97	3	115	5.2	49	19.29	32	38				
8. R. T.	G	100	4.4	35	15.04	3	94	4.48	34.5	15.51	30	40	94	4.4	35	15.80
9. P. K.*	G	90	4.5	34	16.95	3	86	4.4	35	16.88	15	15	80	4.1	33	12.00

*Exploratory thoracotomy only.

See Table IV for explanation of abbreviations.

TABLE VII

BRONCHIECTASIS; CONDITION OF THE ARTERIAL BLOOD BEFORE, DURING, AND FOLLOWING THE RESECTION OF LUNG TISSUE IN 10 PATIENTS

PATIENT	PREOPERATIVE							DURING OPERATION						POSTOPERATIVE			
	CONDITION	HB. (%)	R.B.C.	HMCRT.	BLOOD O_2	V.C.	O.T. (HR.)	HB. (%)	R.B.C.	HMCRT.	BLOOD O_2	O_2 GIVEN A	O_2 GIVEN B	HB. (%)	R.B.C.	HMCRT.	BLOOD O_2
Ethylene + O_2 Anesthesia																	
1. M. G.	F	86	4.1	33	16.09	2100	2	82	4.0	30	10.92	10	14				
2. F. U.	P	98	4.38	37.5	18.16	3000	3¼	102	4.2	39	11.66	35	35				
3. F. M.	F	96	4.68	41	19.62	2900	2¼	104	4.7	42	12.44	20	25	86	4.5	30	14.17
Ethylene + O_2 + Ether Anesthesia																	
4. D. G.	P	90	4.0	49	15.16	2100	2	94	4.5	50	13.31	37	38	90	3.9	44	14.00
5. J. C.*	F	96	4.9	35	17.03	—	1½	90	4.8	33	15.52	18	20	92	4.6	31	14.75
6. M. S.	F	100	4.5	46	15.02	2600	2	105	4.8	47	14.77	20	25	95	4.2	42	15.97
7. H. F.	G	85	4.3	46	15.51	2500	1¾	86	4.2	47	15.59	25	23	70	3.9	38	14.98
8. D. H.	F	96	4.47	36	19.33	1900	2¾	94	4.4	35	12.88	40	32	80	4.0	30	12.88
9. M. B.	F	90	4.9	37	16.07	1850	2	88	4.8	36	12.88	25	24	84	4.5	34	14.02
10. G. N.†	P	94	4.75	35	14.79	1250	2	92	4.6	36	8.43	25	35	84	4.2	32	14.53

*Infected cystic disease of the lung.

†Bilateral chronic inflammation of the lung.

During the operation, arterial blood was obtained just before closure of the pleural cavity. The condition of the patient is given as G-good, F-fair, or P-poor. Abbreviations: Hb., hemoglobin; R.B.C., red blood cells; Hmcrt., hematocrit; O_2, oxygen; V.C., vital capacity, O.T., operating time in hours; Oxygen given, A—average per cent during the entire operation, B—per cent of oxygen being given when arterial blood sample was obtained.

TABLE VIII

MISCELLANEOUS INTRATHORACIC OPERATIONS

PATIENT	PREOPERATIVE						DURING OPERATION						POSTOPERATIVE			
	CONDITION	HB. (%)	R.B.C.	HMCRT.	BLOOD O_2	O.T. (HR.)	HB. (%)	R.B.C.	HMCRT.	BLOOD O_2	O_2 GIVEN A	O_2 GIVEN B	HB. (%)	R.B.C.	HMCRT.	BLOOD O_2
MEDIASTINAL CYSTS OR TUMORS																
Ethylene + O_2 Anesthesia																
1. A. G.	G	92	4.1	38	16.85	2¼	90	4.3	37	15.36	23	29	78	4.0	34	14.48
Ethylene + O_2 + Ether Anesthesia																
2. E. S.	G	106	5.2	44	18.16	2	108	5.0	44	21.52	15	25	102	5.0	42	15.53
3. L. C.	F	88	4.9	38	16.01	3¾	84	4.8	38	16.33	25	25	94	4.8	35	17.88
OPERATIONS ON THE HEART OR GREAT VESSELS																
Ethylene + O_2 Anesthesia																
4. E. G.	F	98	5.2	38	19.30	3	100	5.0	37	17.34	18	19	80	4.0	30	12.41
5. K. H.	F	90	5.0	37	18.12	2¾	90	4.9	36	14.85	13	13	70	4.0	26	11.58
Ethylene + O_2 + Ether Anesthesia																
6. S. C.	P	90	4.0	33	10.40*	2	90	4.0	33	14.60	34	36	100	3.8	32	15.91

*Drawn during induction; patient was receiving 20 per cent oxygen.

See Table IV for explanation of abbreviations.

during the operation due to the marked anemia present. Patient No. 4 had considerable silicosis in both lungs and showed definite lowering in arterial blood oxygen during the operation despite the fact that the anesthetic mixture contained a high percentage of oxygen. No other patient in this group showed evidence of anoxia. The amount of oxygen in the anesthetic mixtures varied from 15 to 41 per cent. Except for patient No. 4 there was little difference between the preoperative and operative levels of oxygen in the arterial blood. The group was divided almost equally as to the anesthetic agents used, four receiving ethylene plus oxygen, and the remaining five, ethylene plus oxygen plus ether. With the exception of the influence of anemia and the poor general condition of the patients, there appeared to be little difference in arterial blood oxygenation between these two groups. The findings in the postoperative arterial blood samples will be discussed later.

Bronchiectasis (Table VII).—Although ten patients are included in this group, the diagnosis in patient No. 5 was infected congenital cystic disease of the lung and in patient No. 10 chronic inflammation of the lung (bilateral). Of all the groups of patients in this study the present group was by all odds the most difficult to manage from the standpoint of preventing anoxia. An analysis of Table VII revealed several factors contributing to this difficulty. The general condition of the patient was poor in most cases. Some of the patients had moderate to severe anemia. The vital capacity was definitely reduced in almost all, and extremely so in one (No. 10). In addition, most of these patients were more or less toxic due to the infection of the lungs. Patients Nos. 1, 2, 3, 4, and 10 had bilateral involvement of the lung. Only three of this group received ethylene plus oxygen as the anesthetic mixture, the remainder receiving ether in addition. Most of these patients were given a higher percentage of oxygen than those in the other groups in this study, the percentage of oxygen ranging from 15 to 40, the average being 27 per cent. In spite of this fact more patients of this group had a reduction in arterial blood oxygen during the operation (as compared to the preoperative level) than those of any other group. In some cases this reduction was extreme, for example, patients Nos. 2, 3, 8, and 10. Cyanosis was observed in some of these patients.

The duration of operation in this group averaged approximately two hours. Aspiration of secretions from the tracheobronchial tree, or waiting for improvement of the patient's condition before continuing with the operation, consumed a part of this time.

There was a noticeable difference in the behavior of the patients with unilateral infection as compared to those with involvement of both lungs. This is demonstrated by patients Nos. 5, 6, and 7 with unilateral involvement, who showed little or no reduction in arterial blood oxygen during the operation as compared to that of the preoperative levels. These patients were also less anemic and needed less oxygen during operation than the bilateral cases; thus indicating that the extent

and distribution of the disease was the major factor in the marked lowering in blood arterial oxygen during operation in the bilateral cases.

The condition of the arterial blood following operation will be discussed later.

Miscellaneous Intrathoracic Operations (Table VIII).—

Mediastinal Cysts or Tumors: Only three patients were studied. The general condition was quite good in all three. The operation lasted an average of two and one-half hours. None of these patients were anemic and the preoperative arterial blood oxygen was fairly normal. There was little or no reduction in blood oxygen during the operation. The percentage of oxygen used in the anesthetic mixture averaged around 26. One of the three patients received ethylene plus oxygen, while in the other two ether was added. There was little difference noted between the two anesthetic mixtures with regard to the level of blood oxygen.

Operations on the Heart and Great Vessels: This group included two patients in whom partial pericardectomy was performed and in both cases the pleural cavity was opened. The third case was a transpleural ligation of a patent ductus arteriosus (and subacute bacterial endarteritis). Only the latter of these three revealed an anemia and this was quite marked. In the former two cases the blood oxygen was relatively normal prior to operation but in the latter (Case No. 6) the arterial blood oxygen was only 10.4 volumes per cent. In spite of this there was no cyanosis, due to the degree of anemia present. Following closure of the ductus, and before closing the pleural cavity, the arterial blood oxygen had become elevated about 45 per cent over the preoperative level.

One of the pericardectomies (patient No. 5) showed some lowering of blood oxygen during the operation. This patient had received ethylene plus 13 per cent oxygen as the anesthetic mixture.

The postoperative arterial blood values will be discussed later along with the other groups.

DISCUSSION OF RESULTS

It is obvious from the above presentation of the results obtained that several factors were contributory in the production of anoxia in these intrathoracic operations. Several of these factors were present in some of the groups of patients, whereas in others they appeared to be less prominent. In order to bring out the importance of various factors involved, a comparison of the results of blood studies in different patients was made.

General Condition of the Patient.—It is obvious from Table IX which presents the results in four patients, two designated as good risks and two as poor risks, that this factor alone plays a major role in the production of anoxia. With other factors being equalized as well as possible, the good-risk patients (S. S. and E. S.) revealed no evidence of

anoxia or of reduction of arterial blood oxygen during the operation as compared to the preoperative level. On the other hand, the poor-risk patients (F. U. and M. L.) developed in one case marked reduction in blood oxygen during the operation as compared to the preoperative level and in the other a small reduction. The first of these patients was cyanotic; but the second, due to the anemia present, showed no evidence of cyanosis.

TABLE IX

INFLUENCE OF GENERAL CONDITION IN PRODUCTION OF ANOXIA

	GOOD				POOR			
	6. S. S. (V)		2. E. S. (VIII)		2. F. U. (VII)		2. M. L. (VI)	
	PREOP.	OP.	PREOP.	OP.	PREOP.	OP.	PREOP.	OP.
Hb.	94	92	106	108	98	102	90	88
R.B.C.	4.2	4.1	5.2	5.0	4.4	4.2	4.8	4.8
Hemat.	38	34	44	44	37	39	32	31
Oxygen		24		28		35		40
Oxygen Av.		20		20		35		40
Blood O_2	16.75	17.01	18.16	21.52	18.16	11.66	11.64	11.10

The patient's number, initials, and table from which taken are indicated. Note the lack of anoxia during operation in the good-risk patients as compared with the poor-risk cases.

Abbreviations: Hb., hemoglobin; R.B.C., red blood cells; Hemat., hematocrit; Oxygen, oxygen received by patient at the time the blood sample was drawn; Oxygen average, average percentage of oxygen received during the entire operation; Blood O_2, arterial blood oxygen.

Local Disease.—As mentioned in the discussion of the results shown in Table VII patients with suppurative disease of the lung developed anoxia or at least a lowering of arterial blood oxygen during operation far more than patients with any other intrathoracic condition. These patients usually had some reduction in respiratory reserve. The disease condition had been present usually for a number of years, thus putting a strain on the heart. Most of these patients had a low-grade fever thus showing some degree of toxicity. All of these factors probably contributed in the reduction of tolerance to endure an intrathoracic operation. On the other hand, patients with mediastinal tumors or cysts, patients receiving operations for essential hypertension, and patients with carcinoma of the esophagus, cardia, or lung where no infection was present revealed little evidence of arterial blood oxygen reduction during an intrathoracic operation.

Condition of the Blood.—The results seen in Table X demonstrate the influence of anemia on arterial blood oxygen. The normal patient (C. P.) showed no change in the arterial blood oxygen taken during operation as compared to the preoperative reading, both being within the normal limits. This patient received an anesthetic mixture containing only 13 per cent of oxygen during the operation. Patients A. M. and A. P. showed a considerable anemia prior to operation, with marked reduction in arterial blood oxygen. Neither of these patients was cyanotic during the operation, although the arterial blood oxygen was under the cyanosis level, thus indicating that in anemic patients cyanosis is a poor sign to expect as an indication of anoxia. Unfortunately,

TABLE X

INFLUENCE OF DISEASE CONDITION ON THE PRODUCTION OF ANOXIA

	MEDIASTINAL TUMOR 1. A. G. (VIII)		HYPERTENSION 3. J. L. (IV)		CAR. OF THE LUNG 8. R. T. (VI)		BRONCHIECTASIS 3. F. M. (VII)	
	PREOP.	OP.	PREOP.	OP.	PREOP.	OP.	PREOP.	OP.
Hb.	92	90	100	96	100	94	96	104
R.B.C.	4.1	4.3	5.1	4.9	4.4	4.4	4.7	4.7
Hemat.	38	37	35	34.5	35	34.5	41	42
Oxygen		29		20		40		25
Oxygen Av.		23		20		30		20
Blood O_2	16.85	15.36	18.82	18.96	15.04	15.51	19.62	12.44

The patient's number, initials, and table from which taken are indicated. Anoxia was seldom observed during operation in the first three groups of patients but was often present in the bronchiectasis patients.

See Table IX for abbreviations.

it is in an anemic individual that early signs of anoxia must be recognized in order to prevent disastrous results. The blood oxygen during operation was actually slightly higher than the preoperative level, although the anesthetic mixture contained only 15 per cent oxygen.

Anesthetic Agent.—Most of the patients in this study received either ethylene plus oxygen or ethylene-oxygen plus ether. With the exception of the group in Table VII (bronchiectasis), little difference was noted between the two anesthetic mixtures in the maintenance of satisfactory blood oxygen during the operation. It was soon noticed that an increase in the percentage of oxygen given would not necessarily compensate for other factors which tended to produce anoxia. Ether added to ethylene-oxygen was of definite advantage in the production of deeper anesthesia without reduction of the percentage of oxygen below the desirable level. Taking the groups of patients as a whole, 17 to 20 per cent oxygen was found adequate for the prevention of anoxia.

Influence of the Duration of the Operation on the Production of Anoxia.—That long operations are much more poorly tolerated than short ones, an impression that has long been prevalent, was not substantiated by this study. When other factors which are influential in the production of anoxia were controlled, long operations were tolerated as well as the shorter ones. In this series of patients the operating time varied from approximately one and one-half to four hours. Examples of various durations of operation are as follows: (1) One and one-half hours, P. L. (No. 2), Table IV; (2) two hours, H. L. (No. 8), Table V; (3) three hours, P. K. (No. 9), Table VI, and (4) four hours, P. A. (No. 12), Table V. In each of the above four patients, oxygenation of the arterial blood near the end of the operation was as good or better than before the operation although the operation in patient No. 4 lasted almost three times as long as that of No. 1. In order to obtain these results, attention was given to the replacement of blood loss and to the maintenance of sufficient cardiorespiratory function.

It is fortunate that long operations may be well tolerated, for undue haste in some intrathoracic procedures would not be for the good of the patient.

TABLE XI

DECREASED O_2 TRANSPORTING MEDIA IN THE PRODUCTION OF ANOXIA

	NORMAL		ANEMIA			
	9. C. P. (V)		1. A. M. (V)		5. A. P. (IV)	
	PREOP.	OP.	PREOP.	OP.	PREOP.	OP.
Hb.	100	102	76	80	70	74
R.B.C.	4.9	4.9	4.0	4.2	4.2	4.3
Hemat.	40	40	34	35	27	30
Oxygen		13		15		15
Oxygen Av.		13		15		15
Blood O_2	18.01	17.98	12.57	13.81	10.91	11.26

Patient's number, initials, and table from which taken are indicated. A similar degree of anoxia before and during operation was observed in these patients.
See Table IX for abbreviations.

Bronchial Obstruction and Decreased Vital Capacity.—It has already been mentioned that intrathoracic operations for suppurative disease of the lung such as bronchiectasis and lung abscess were the least well tolerated in this series of patients. Three major factors play an important part in the production of anoxia in this group of patients, viz., (1) decreased vital capacity, (2) bronchial obstruction, and (3) some degree of toxicity. In addition, many of these patients have considerable anemia. In the group of ten patients studied the average preoperative arterial oxygen level was only 16.7 volumes per cent and in seven of these a fall of from 2 to 7 volumes per cent resulted during the operation in spite of the fact that a high per cent of oxygen was used in the anesthetic mixture, and that blood transfusions were being given during the operation. Several of these patients (five) had bilateral disease and in these the lowering of blood oxygen during operation was more severe. Some of these patients were not cyanotic and revealed no other obvious signs of anoxia until the blood was analyzed. When the preoperative blood oxygen is as low as 14 or 15 volumes per cent in the presence of an anemia an alarming degree of anoxia may result before obvious signs or symptoms are manifest.

Obstruction of the air passages during operation may be considerably obviated by postural drainage both before and during operation and by bronchoscopic aspiration at the conclusion of the operation. This routine has usually been used in our patients. In a few patients an endotracheal catheter was employed during the operation. In spite of the previously mentioned precautions, some obstruction of the air passages by secretions, blood, or pus is apt to occur and interfere with ventilation of the blood. Reduction in blood oxygenation by poor ventilation cannot be completely compensated for by increasing the percentage of oxygen in the anesthetic mixture used. Blades and Graham[20] have thought it advisable to elevate the head of the table during operation in patients with bilateral bronchiectasis. The secretions from the upper lobes then tend to drain into the lower lobe of the dependent side, thus keeping the trachea clear. At the conclusion of the operation, bronchoscopic aspiration of the accumulated secretions is carried out.

TABLE XII

POSTOPERATIVE ANOXIA IN 4 PATIENTS WITH NORMAL BLOOD OXYGEN BEFORE AND DURING SURGERY

	12. P. A. (V)			4. S. C. (V)		
	PREOP.	OP.	P.O.	PREOP.	OP.	P.O.
Hb.	114	110	100	90	94	80
R.B.C.	5.2	5.1	5.2	4.8	4.7	4.4
Hemat.	42	41	32	40	40	32
Oxygen		40			15	
Oxygen Av.		37			15	
Blood O.	19.17	21.52	13.69	19.40	17.35	14.62
	1. A. G. (VIII)			5. B. H. (V)		
	PREOP.	OP.	P.O.	PREOP.	OP.	P.O.
Hb.	92	90	78	116	114	82
R.B.C.	4.1	4.3	4.0	5.0	4.7	4.5
Hemat.	38	37	34	46.5	47	32
Oxygen		29			15	
Oxygen Av.		23			15	
Blood O.	16.85	15.36	14.48	20.98	20.81	15.35

The patient's number, initials, and table from which taken are indicated. Twelve of forty-four patients studied, or 27.2+ per cent, showed similar results.
See Table IX for abbreviations.

Postoperative Anoxia in Patients Having Normal Blood Oxygen Before and During Operation.—In the above series of patients twelve of forty-four revealed a reduction in blood oxygen in the postoperative samples where the preoperative and operative blood oxygen was normal. Six of these were in the group of patients with carcinoma of the esophagus or stomach, three in the miscellaneous intrathoracic operations, two in the hypertension group, and one patient had bronchiectasis. The remaining seven of the fifty-one operations had no postoperative blood oxygen determinations. Except in the case of bronchiectasis most of the postoperative reduction in blood oxygen occurred in groups where little or no fall occurred during the operation. The significance of this is obvious in that a patient who appeared to have gone through an operation with little or no difficulty might be less observed during the postoperative period and the ill effects of the subsequent drop in blood oxygen be unobserved until serious consequences had occurred. In Table XII are presented data concerning four patients in whom reduction in blood oxygen occurred following operation although it had remained normal during the operation. It will be noted that this fall was extreme in three of the four cases, approximately 5 volumes per cent. Since the preoperative and operative levels were quite good in these cases, the postoperative fall led to no serious difficulties.

The explanation for this reaction was not entirely clear. It was accounted for in part by the oozing of blood within the pleural cavity following operation, but the amount of blood loss was insufficient to explain the degree of anoxia. Examination of the blood showed that it was due in part to the development of hypochromatic anemia. It was quite evident that the red cell count is least reliable for determining the state of the oxygen transportation media. The hemoglobin values were more reliable and the hematocrit most accurate in this regard.

Thus, it is evident from the above studies that several factors may contribute to the production of anoxia both during and following intrathoracic operations. Also, that the ill effects of one or more factors might not be entirely compensated by improving the patient otherwise. Attention should be given to the various steps in the transportation of oxygen from the inhaled gas to the tissues and it should be ascertained that the organs are functioning properly before an operation is done. This will include transfusion of blood in patients with anemia, improvement of the nutritional state of patients with esophageal obstruction, and postural or bronchoscopic drainage for patients with pulmonary infection. During the operation, blood transfusion will maintain a more nearly normal oxygen transporting medium in the blood and postural drainage will help to maintain a patent airway.

The question of anesthesia mixtures continues to be a subject of considerable controversy. We are in agreement with Churchill and Beecher[9] that ether appears to have no more harmful effects than ethylene or cyclopropane in these patients. Since ethylene is rapid and pleasant for induction, is non-irritating, is administered in a physiologically normal amount of oxygen, and is undisturbing to the cardiac mechanism, we have considered it somewhat more advisable and have added ether vapor when indicated in sufficient amounts to obtain the desired depth of anesthesia. It has been well demonstrated by these recorded studies that a high percentage of oxygen in the anesthetic mixture does not necessarily mean that the blood oxygen levels will be correspondingly increased. From the studies made, it appeared that from 17 to 20 per cent oxygen in the anesthetic mixture was sufficient for satisfactory oxygenation of the blood in all except the patients with bronchiectasis or other suppurative processes of the lung. In these patients a higher percentage of oxygen is desirable, but it should not be the source of false security. To have administered 50 to 60 per cent of oxygen in the anesthetic mixture does not necessarily mean that the patient is able to make use of the oxygen received.

SUMMARY AND CONCLUSIONS

1. An investigation of the incidence of anoxia both during and following intrathoracic operations has been made in forty-five patients (fifty-one operations).

2. The operations were made for carcinoma of the lung (9); mediastinal tumors or cysts (3); malignant hypertension (8); constrictive pericarditis (2); bronchiectasis (10); carcinoma of esophagus or stomach (12), and patent ductus arteriosus (1).

3. Ethylene-oxygen or ethylene-oxygen plus ether anesthesia administered under mild positive pressure (4 to 8 mm. Hg) through a snug fitting face mask was employed in most cases.

4. Anoxia was seldom observed during the operation in patients who had no infection of the lung. Factors which played a major part in

influencing the development of anoxia included: the general condition of the patient, the state of the blood, the local disease, bronchial obstruction, and decreased vital capacity.

5. The duration of the operation and the anesthesia appeared to have little influence on the production of anoxia when the above contributory factors were controlled. Ether when added to ethylene-oxygen produced deeper anesthesia with associated adequate oxygenation. The administration of a high percentage of oxygen in the anesthetic mixture may give a false sense of security if sufficient attention is not given to the other factors which play a part in the production of anoxia.

6. Of fifty-one operations, the blood oxygen level before, during, and following surgery remained normal in twenty-one, but was reduced during operation in fourteen. Postoperative reduction in blood oxygen with unchanged blood oxygenation during surgery was observed in twelve out of forty-four patients (27.2 per cent) in whom postoperative studies were made.

7. The hematocrit reading was a much better index than the red cell count or hemoglobin value for the determination of the true state of oxygen transporting medium.

8. There were six postoperative deaths, none apparently related to the anesthesia employed. Three deaths were on the basis of cardiac failure, a fourth was due to anuria following the use of sulfanilamide, a fifth was due to pneumonia following lobectomy on a very poor-risk child for bilateral bronchiectasis, and the sixth due to massive empyema with leak of the anastomosis following resection of the cardia.

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SILVER PLUG AS A METHOD OF BRONCHIAL CLOSURE IN EXPERIMENTAL PNEUMONECTOMY

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THE lack of a method of permanently closing the stem bronchus was one of the most important factors in delaying the advent of the first successful total pneumonectomy for bronchiogenic carcinoma in 1933, which was performed by Graham.[1] In the past decade the operative mortality has steadily decreased from a relatively prohibitive 50 per cent to from 20 to 25 per cent in pneumonectomy, exclusively for bronchiogenic carcinoma. The latter mortality rate is for a series of cases of forty or more. Pneumonectomy for a smaller series of cases or one including other conditions carries an even lower operative mortality rate. Opening of the stem bronchus has been the major cause contributing to the excessively high mortality rate. A tremendous amount of experimental work has been done endeavoring to solve this problem. Rienhoff,[2] Adams,[3] and others have contributed to this problem both clinically and experimentally; the former has written a very comprehensive survey of the literature in his last publication.

Experimental methods to have even the slightest value must, if successful, be capable of metamorphosis into the realm of clinical usage and applicability. Following so closely upon Rienhoff's comprehensive monograph concerning closure of the bronchus in total pneumonectomy, it would seem very apparent that there is little to add. However, a review of the literature on bronchial closure and conclusions drawn from clinical and experimental work have pretty well settled two things. One, that most experimental work on this subject falls short because of not being clinically applicable; infection in the clinical cases and lack of the same in the dog's tracheobronchial tree is the essential difference. Two, healing of the bronchial stump occurs at a site of predilection which, in the great majority of instances, is the distal end of the bronchus, and this in spite of the type, number, or location of any or all varieties of occluding materials or tissues. The use of a silver plug as a method of bronchial closure after experimental lobectomy has been reported previously by Rosenthal and his associates.[4] In the present experimental work being reported it has been used as a method of bronchial closure after total left pneumonectomy in twenty-seven normal dogs. At the time of this presentation, similar experimental work is being carried out

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on dogs with suppuration in the left lung. This is introduced bronchoscopically by insufflating the foul sputum of bronchiectatic patients. It is hoped that this second group will allow a more critical evaluation of the effectiveness of this method, especially as to its clinical application.

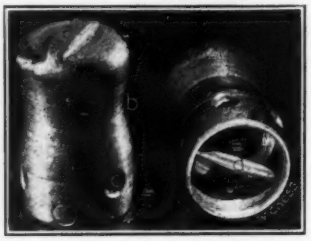
Graham has stated that the virulent type of infection present is very instrumental in producing the high incidence of bronchopleural fistula postoperatively. He also emphasizes that if simultaneously total thoracoplasty could be done safely, in order to obliterate the potential empyema space, then he did not think that closure of the stump would continue to be anything of major importance. Rienhoff has reported the occurrence of bronchopleural fistula in sixteen of sixty-one total pneumonectomies or 26.2 per cent. Ochsner[5] has had a failure of closure of the stem bronchus in three of thirty-two total pneumonectomies for pneumoplastic diseases, with an incidence of approximately 9 per cent. Shenstone[6] has noted only one open fistula develop in twenty-three consecutive total pneumonectomies for a minimal 4 per cent. With the exception of the last two series cited, it is very obviously apparent that bronchopleural fistula in total pneumonectomy is still the important factor.

In this series of twenty-seven experimental pneumonectomies using a silver plug as a method of bronchial closure, there were five deaths. Only three were considered as resulting from the bronchus opening. In the other two the bronchus remained closed. The plug was removed bronchoscopically in the twenty-four animals surviving, at intervals varying from fourteen days to over twelve months. The three deaths due to the plug being coughed up by the animals happened within the first two weeks postoperatively. These fatalities occurred early in the series because silver plugs of correct size were not available and the plugs used were too small. In the last ten animals operated upon there have been no deaths.

EXPERIMENTAL TECHNIQUE

Normal dogs averaging approximately 8 kg. were operated upon under intraperitoneal nembutal and positive pressure anesthesia. Total left pneumonectomy was performed in twenty-seven animals using the following technique. The usual incision in the fourth left interspace was utilized, cutting across the fibers of the latissimus dorsi muscle; however, in the last five experiments the gridiron incision was used. The pulmonary vessels were individually and doubly ligated with a fine braided black silk. A purse string of silk was sutured around the left stem bronchus about 1 to 1½ cm. distal to the carina. A silver plug as described in Fig. 1 (*A*) was then inserted into the lumen of the stem bronchus through a 1 cm. transverse incision in the secondary bronchi. The purse string was then tied snugly around the groove in the middle third of the silver plug, before cutting away the entire left lung (Fig 1, *B*). The lung was removed 1 to 5 mm. distal to bifurcation of the stem bronchus. A flap of tissue 5 mm. in width by 4 mm. in length was

fashioned from the septum bifurcating cartilaginous portion of the stem bronchus and sutured to the distal end of the plug as in Fig. 2. The intrabronchial space distal to the silver plug was filled with sulfanilamide and closed with four mattress sutures of silk. About 3 Gm. of sulfanilamide were left in the pleural cavity before closing. No attempt was made to cover the end of the bronchus with mediastinal pleura. Two pericostal sutures of silk were tied and the wound closed in layers after overinflating the opposite lung. Two grams of sulfanila-



A. *B.*

Fig. 1.—*A*, Lateral view of silver plug illustrating ridge on distal end with perforation for suturing membranous flap to (*a*); groove around distal third of plug (*b*); perforations in proximal third for drainage (*c*).

B, View of the proximal end as seen bronchoscopically, demonstrating crossbar necessary for removal (*d*).

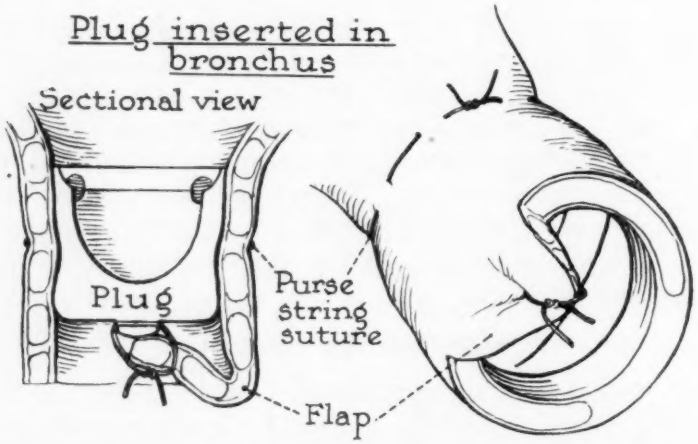


Fig. 2.—Sectional view of silver plug in stem bronchus; distal end of stem bronchus showing silver plug held in place by tied purse-string suture. Flap was fashioned from wall of bronchus as shown or septum bifurcating stem bronchus.

mide were spread throughout the wound proper. The cutaneous sutures were removed routinely on the eighth postoperative day. The silver plug was removed bronchoscopically at intervals post operatively, varying from fourteen days to more than twelve months.

RESULTS

1. Twenty-four of the twenty-seven normal dogs upon whom total left pneumonectomy was performed survived the operative procedure (Table I). Two additional deaths occurred secondarily to operation (see below).

TABLE I

TOTAL LEFT PNEUMONECTOMY USING SILVER PLUG IN CLOSURE OF BRONCHUS

DOGS OPERATED	OPERATIVE DEATHS		MORTALITY (%)	
	BRONCHUS		BRONCHUS	
	OPENED	REMAINED CLOSED	OPENED	REMAINED CLOSED
27	3	2	11.1	7.4

2. The three deaths occurred six, twelve, and nineteen days postoperatively. The mechanism was apparently due to tension pneumothorax which occurred shortly after coughing up the plug at the times previously cited. These instances happened early in the series because silver plugs too small for the stem bronchus were used. Plugs of correct size were not available.

3. There have been no fatalities in the last ten animals operated upon.

4. The silver plug was removed bronchoscopically at intervals varying from fourteen days to more than twelve months.

5. Bronchoscopically there was rarely any sign of irritation or infection noted around the plug, either before or after removal.

6. The proximal end of the silver plug approximated the carina to within 2 or 3 mm. in all the animals surviving.

7. The plug was rotated with the extracting forceps before removal was attempted bronchoscopically. A small amount of traction was all that was necessary to loosen the plug and attached silk from its bed in the healed distal end of the bronchus. Both the silk purse string and the suture used to anchor the bronchial flap to the perforated distal end of the plug were found attached to the plug in the majority of cases. This agrees with other reports in the literature regarding the occluding sutures cutting through.

8. The areas where the sutures cut through were entirely healed grossly and microscopically.

9. The distal end of the bronchus after the plug was removed appeared clean and showed no evidence of infection. There was a small amount of oozing from the bronchial bed from which the plug was reremoved; however, this ceased spontaneously within a minute or two.

10. The dogs were sacrificed from three to twelve months postoperatively. In every case the bronchial stump was cone shaped and of homogeneous consistency throughout.

11. The heart and diaphragm in all animals had shifted into the pleural cavity of the operated side. The ribs on the left side were slightly compressed. (Fig. 3.)

12. Microscopically (Figs. 4, 5, and 6), the bronchial flap which was sutured to the perforation in the distal end of the plug protruded in to the lumen from the stump. The relationships of mucosa, cartilage, and muscle were the same in the wall of the bronchus as in the stump.

13. The wound in the chest wall was infected in six of the twenty-seven animals. In two of the animals that died, eight and five weeks

postoperatively, the wound infection was interpreted as being responsible. These two deaths occurred five and three weeks, respectively, after removal of the plug. Autopsy revealed a healed and intact bronchial stump.

Fig. 3.—Post-mortem view with anterior chest wall removed in sacrificed animal, thirty days after plug removal, showing shift of heart and mediastinum to operated side.

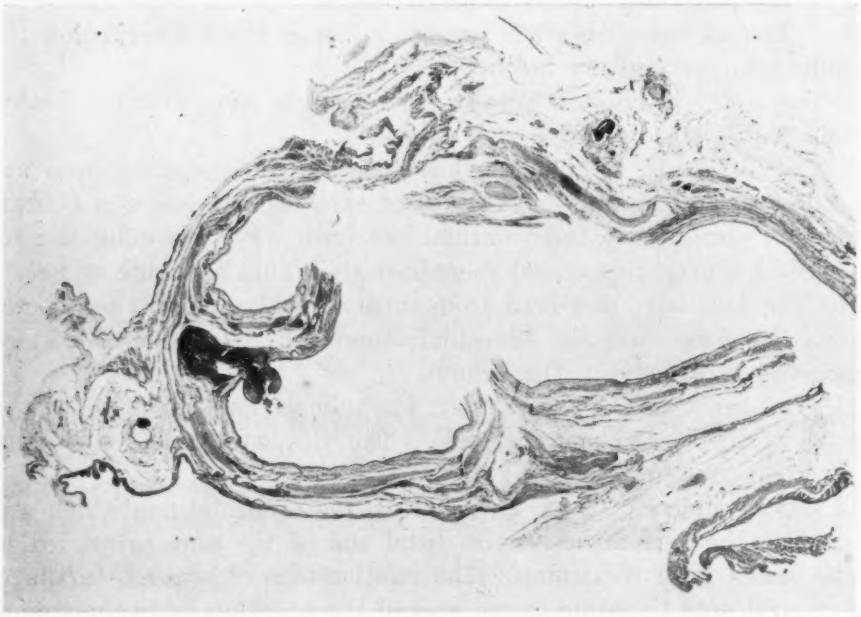


Fig. 4.—Low-power photomicrograph of left stem bronchus (30 days after pneumonectomy—plug removed on sixteenth day postoperatively) showing muscle, cartilage, and mucosa covering distal end and bronchial flap projecting into lumen.

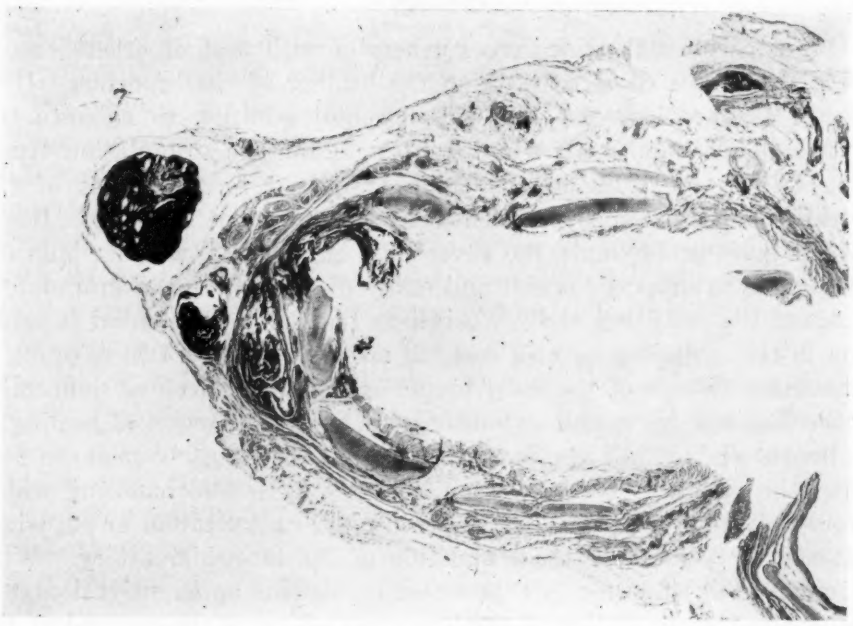


Fig. 5.—Low-power photomicrograph of left stem bronchus, showing narrowing of bronchial lumen proximal to site of silver plug. Retained black silk at distal end.

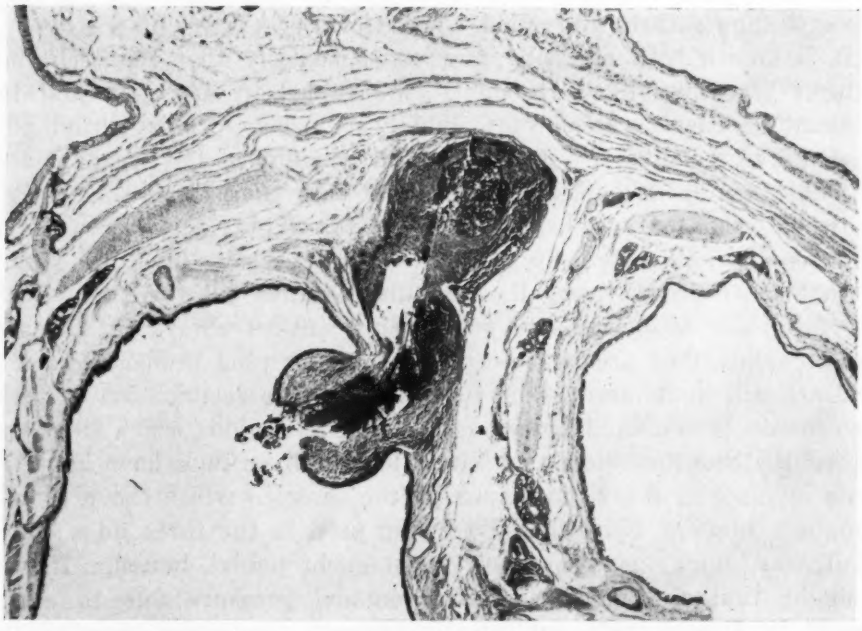


Fig. 6.—High-power photomicrograph of left stem bronchus, as seen in Fig. 4, showing distal stump and bronchial flap with retained silk. Note definite layers of mucosa, muscle, and cartilage completely covering distal stump and united by a narrow zone of scar.

COMMENT

Our experimental work agrees generally with that of others except for a few minor disagreements on the healing of the bronchus. It is offered as a constructive and supplemental addition to enhance the bronchial healing by allowing more time for the granulation tissue plug to become solid before being subjected to the stress of the intrabronchial pressure occasioned by coughing or sneezing. Based primarily on prophylaxis, the silver plug merely adds another bulwark or buttress to support the soft and easily disrupted plug of granulation tissue at the cut distal end. We believe that it might be used in addition to the occluding sutures and the mediastinal pleura in effecting a permanent closure of the stem bronchus in pneumonectomy clinically.

Rienhoff and his associates conclude that the main point of healing is at the cut end. They also state that every effort must be made to preserve the viability of this portion not only by gentle handling which avoids any sort of trauma, such as crushing, cauterization or suturing, but also by preserving the circulation of the bronchial artery. With reference to the latter our purse-string suture apparently does not jeopardize the circulation of the bronchial artery as the cut end of the stump still bleeds after it is tied, and the stump heals. All the bronchial stumps in our animals healed without the aid of mediastinal pleura, the cut end being left free in the pleural cavity. Obviously, in clinical cases the more items that can be used to act as a buffer or stopgap, as the occluding sutures are called, the better.

It is known both clinically and experimentally that the occluding sutures cut through the bronchial wall aided by infection and inflammatory edema after approximately ten days. This period corresponds to the time of occurrence of the opening of the bronchus and its subsequent bronchopleural fistula and empyema. It is during this critical period that we believe that the silver plug may serve as an additional so-called stopgap or buttress and protect the distal stump from "blowing out" after the occluding sutures cut through. Since the distal silk anchoring and purse-string sutures always cut through the bronchus, they are removed with the silver plug bronchoscopically and are still in its groove and perforation. The combination of these two factors plus inflammatory edema and granulations which have narrowed the bronchial lumen proximal to the silver plug have kept the plug in place in every animal except the three in which the plug was coughed up (Fig. 5). The silver plug used in the three dogs which died was much smaller than the stem bronchial lumen. It was thought that the increased intrabronchial pressure due to cough would be transmitted centrifugally through the silver plug to the lateral bronchial wall instead of being concentrated on the weakest part of the granulating stump distally, which like a chain is no stronger than its weakest link. If this is the mechanism and can be made to work clinically, then the distal stump should be protected as long as

need be to become solid, especially during the critical period after the occluding sutures cut through. The silver plugs have been left in many months without any apparent deleterious results.

The problem of the virulence of the infection clinically and whether or not the lowered plasma protein and ascorbic acid levels in patients with carcinoma of the lung will allow optimum healing conditions is another uncontrollable factor to be contended with, as emphasized by Graham. It is hoped that, by continuing these experiments in dogs with artificially produced purulent bronchitis, the value of the silver plug in an infected field will be proved or disproved.

Another method of support for the bronchial stump is the chest wall which will fall in after total or subtotal thoracoplasty as used by Graham on the first total pneumonectomy. However, he considers this unsafe as a simultaneous procedure. Whether a selective paravertebral thoracoplasty simultaneously over the stem bronchus will allow enough of the chest wall to fall in to act as a pedicle flap for adequate support is something for conjecture. Graham's original intention was to obliterate the pleural space entirely, in the absence of which an empyema could not form.

The deaths of the two animals which died as a result of wound infection, wound disruption, and open pneumothorax were attributed to the skin sutures being inadvertently left in the wound indefinitely. These deaths occurred three and five weeks after plug removal and were not considered operative deaths. The bronchial stumps in both were solidly healed.

It is our supposition, theoretically, that if occluding sutures and mediastinal pleura will allow a bronchopleural fistula incidence of 25 per cent or less after total pneumonectomy clinically, then the additional support offered by the silver plug plus a selective paravertebral thoracoplasty should decrease the incidence proportionately.

The blowing to-and-fro of air during respiration must be prevented to allow the all-important cut end time to heal. The marked accentuation of this unwanted mechanism by coughing during the critical period we consider might be better obviated by the addition of the silver plug and other supportive measures as mentioned.

In the twenty-four animals in which the plug remained intact postoperatively, no bronchopleural fistula occurred either before or after removal of the plug.

SUMMARY

1. Total left pneumonectomy was performed in twenty-seven normal dogs using a silver plug as a method of bronchial closure.

2. There were three postoperative deaths due to the plug being coughed up within two weeks postoperatively. These deaths occurred early and were due to the fact that the silver plug was too small and did not fit the bronchus snugly. Therefore, the plug must be of the correct size.

3. In the last ten animals there have been no fatalities.

4. The twenty-five dogs surviving total left pneumonectomy had the silver plug removed bronchoscopically at intervals postoperatively, varying from 14 to over 300 days.

5. After the silver plug had been removed bronchoscopically, the animals were sacrificed at different periods after removal to note the method and solidarity of the healed bronchial stump.

6. The distal end of the bronchus as seen through the bronchoscope after removal of the plug and as viewed through the pleural cavity postmortem, appeared healed and revealed no sign of infection.

7. Bronchopleural fistula tested for in the usual manner was entirely negative. Microscopic sections verified the solidarity of the healing and the absence of infection.

8. Healing occurred at the line of suture in the distal end of the bronchus. The healed end of the bronchus was conical in shape in the majority of animals.

9. Two dogs died thirty-four and twenty-one days after removal of the plug from an infected wound. The bronchial stump was well healed and showed no sign of infection.

10. This experimental work is being continued with suppuration distal in the left lung.

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THE PROTEIN AND FLUID BALANCE IN EXPERIMENTAL SHOCK PRODUCED BY INTESTINAL TRAUMA

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A FUNDAMENTAL factor in the development of hematogenic shock is the decrease in the effective circulating blood volume. There is considerable discussion as to whether a local loss of fluid at the site of injury can account for the blood volume depletion. The experiments of Blalock[1] and Phemister and Parsons[6] support this hypothesis. The advocates of the "traumatic toxemia" theory[2] believe that there is a generalized as well as a local fluid loss, but definite evidence of a circulating toxin which initiates generalized capillary damage has not been demonstrated. Many investigators now believe that traumatic shock develops as a result of combined local and general fluid depletion, but have not found a specific cause.

In attempts to solve this problem, previous experiments have been concerned largely with fluid changes measured in terms of the increase in weight of the traumatized tissues. The nature and amount of the plasma protein lost from the circulation has received less attention. It is hence important that experiments be undertaken in which the plasma protein as well as the fluid loss be determined. The experiments which are described were performed in an effort to trace both the protein and fluid loss.

In experimental shock produced by standardized intestinal trauma it is possible to collect quantitatively the protein and fluid lost at the site of injury. In this type of shock most of the fluid and protein which are lost from the circulation can be recovered at the site of trauma. This loss occurs both from the serosal surface of the bowel and as extravasation into the bowel wall and its mesentery. The average protein concentration in the fluid lost from the bowel is 4.32 Gm. per cent. The fluid contains a proportionately greater amount of albumin than that found in the normal circulating plasma. The amount of plasma lost from the circulation increases proportionately with the survival time of the animal. The protein concentration of the plasma, and, hence, its specific gravity, decrease as shock develops.

In a previous publication a comparison was made of the relative efficacy of various concentrations of plasma in treating experimental shock due to intestinal trauma.[4] In these experiments, as in the current

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treatment of clinical shock, large amounts of plasma were used. An attempt has been made to determine the protein balance in treated dogs, but in the majority of experiments a large amount of the injected plasma cannot be accounted for at the site of trauma. Those animals treated with half-dilution plasma (plasma diluted with an equal quantity of saline solution) most closely approach a fluid and protein balance.

METHODS

All dogs were normal healthy animals obtained from stock. They were followed for a period of two weeks or more before the experiments in order to insure a normal food intake and fluid balance. The technique of the production of shock by intestinal trauma has been discussed at length in a previous publication.[4] Blood volumes were obtained using the blue dye, T-1824. All protein determinations were carried out in duplicate or triplicate by micro-Kjeldahl analysis. Specific gravity determinations were made by both gravimetric and falling-drop techniques, one method giving satisfactory check on the other. Bowel analysis was made in the following manner. After death of the animal, clamps were placed across the bowel and at the root of the mesentery in order to retain all blood and fluid in the traumatized area. The bowel was resected between clamps, transferred to a 3,000 c.c. beaker, and weighed. The bowel was then opened and all foreign material, including parasites, removed. About 2,000 c.c. of distilled water were then added followed by 75 c.c. of concentrated sulfuric acid. Digestion of this mixture was carried out overnight in a water bath followed by a 12-hour cooking over a low flame with constant mechanical stirring. At the end of this time a dark uniform mixture was obtained. This was analyzed for nitrogen by the macro-Kjeldahl procedure, the triplicate results agreeing within 0.5 per cent. Samples were then analyzed in triplicate for iron by a modification of the o-phenanthroline method of Schales using the photoelectric colorimeter. Close agreement was found between analysis of the crude digestion mixture and that found after digestion with nitric and perchloric acids. Using the results obtained in the iron determination the total amount of hemoglobin in the entire specimen could be determined. This was deducted from the total value of the bowel protein to allow for the red blood cells in the specimen. All balance studies included the total amount of protein and fluid lost from the serous surfaces, that lost into the bowel, and that removed in sampling.

EXPERIMENTAL OBSERVATIONS

The survival time of the average dog has varied considerably when shock is produced by intestinal trauma (Table I). Some animals have died two hours after trauma with the classical signs of shock, i.e., a rise in hematocrit, decrease in plasma volume, and a marked fall in arterial blood pressure. Others have survived ten hours or more. The arterial blood pressure always decreases as the shock state develops, but is subject to considerable variation. In some animals the pressure decreased

to a level of 60 to 70 mm. Hg several hours before death; in others, the pressure was maintained around 100 mm. Hg and fell precipitously immediately before death. As is shown in Table I, the dogs which survived the longest maintained the highest pressure. In spite of this tendency to maintain a more normal blood pressure the experiments with survival of more than eight hours showed the most marked increase in hematocrit and the greatest decrease in circulating plasma protein.

The concentration of circulating plasma protein and the specific gravity uniformly decrease in this type of shock. Table II tabulates the actual plasma protein concentration and plasma specific gravity in twenty-two typical experiments. The specific gravity decreases an average of .0015 from the control level to the last determination before the death of the animal. The plasma protein concentration falls an average of 13.77 per cent.

TABLE I

SHOCK PRODUCED BY INTESTINAL TRAUMA

NUMBER OF EXPERIMENTS	SURVIVAL TIME (HR.)	RISE IN HEMATOCRIT (%)	DECREASE IN PLASMA VOLUME (%)	B.P. IN SHOCK (MM. HG)
5	2 to 7	19.6	35.8	45
9	7 to 8	19.4	42.2	85
6	8 to 10	23.3	51.9	98

TABLE II

SHOCK PRODUCED BY INTESTINAL TRAUMA

PLASMA-SPECIFIC GRAVITY AND PROTEIN CONCENTRATION; CONTROL AND SHOCK LEVELS

DOG NO.	INITIAL T.P. CONC.* (GM. %)	FINAL T.P. CONC. (GM. %)	PER-CENTAGE DECREASE	INITIAL SPECIFIC GRAVITY	FINAL SPECIFIC GRAVITY	DECREASE
41-285	5.87	5.58	4.9	1.0267	1.0267	0
41-369	5.57	4.98	10.6	1.0260	1.0250	0.0010
41-416	5.16	4.48	13.1	1.0245	1.0237	0.0008
41-446	5.56	4.82	13.3	1.0258	1.0242	0.0016
41-483	4.84	4.45	8.0	1.0247	1.0243	0.0004
41-511	5.96	5.21	12.5	1.0275	1.0257	0.0018
41-513	5.52	4.52	18.1	1.0263	1.0243	0.0020
41-499	6.79	5.39	20.6	1.0296	1.0258	0.0038
40-268	5.35	3.74	29.9	1.0250	1.0219	0.0031
41-455	5.79	5.59	3.5	1.0266	1.0256	0.0010
41-569	5.72	5.63	1.5	1.0262	1.0259	0.0003
41-551	5.09	4.44	12.8	1.0242	1.0228	0.0014
41-456	6.22	6.05	2.7	1.0271	1.0278	+0.0007
40-156	5.68	5.46	3.8	1.0256	1.0251	0.0005
41-527	5.38	4.30	20.0	1.0248	1.0212	0.0036
41-530	6.10	5.20	14.7	1.0271	1.0264	0.0007
41-556	5.31	4.74	10.7	1.0239	1.0226	0.0013
41-557	5.49	4.83	12.0	1.0240	1.0228	0.0012
41-478	5.83	4.49	22.0	1.0243	1.0233	0.0010
40-202	6.86	5.10	25.6			
40-388	6.56	5.16	21.3	1.0267	1.0227	0.0040
41-67	5.15	3.99	22.5	1.0230	1.0226	0.0004
Average			13.77			0.0015

*Total protein concentration.

The relation of the albumin-globulin ratio of the circulating plasma protein to that of the protein present in the peritoneal fluid is tabulated in Table III. In all of the experiments the albumin-globulin ratio of the peritoneal fluid has been greater than that of the circulating plasma, indicating a preponderant loss of albumin. In twenty typical experiments recorded in Table III the albumin-globulin ratio of the peritoneal fluid is 1.69 times greater than the plasma. The total protein concentration of the fluid averages 4.32 mg. per 100 c.c. The very high protein concentration found in Dogs 41-483 and 41-551 has been, possibly, due to a technical error, but the Kjeldahl analyses were repeatedly checked and consistent results obtained. The albumin-globulin ratio of the peritoneal fluid formed during the first two hours of an experiment is greater than that formed between the third and seventh hour. An increasing amount of globulin is lost during the terminal phase of this type of shock (Table IV). It is of interest to compare the experimental

TABLE III

SHOCK PRODUCED BY INTESTINAL TRAUMA

RELATION OF TOTAL PROTEIN, ALBUMIN, AND GLOBULIN IN PLASMA AND PERITONEAL FLUID

DOG NO.	PLASMA				PERITONEAL FLUID				PER CENT INCREASE
	T.P.	ALB.	GLOB.	A.-G.	T.P.	ALB.	GLOB.	A.-G.	A.-G.
41-416	5.16	3.02	2.14	1.41	3.43	2.39	1.04	2.29	1.62
41-446	5.56	2.70	2.86	0.94	2.77	1.95	0.82	2.38	2.53
41-483	4.84	2.73	2.11	1.29	8.36	5.66	2.70	2.10	1.63
41-511	5.96	2.39	3.57	0.67	5.77	3.36	2.41	1.39	2.07
41-513	5.52	2.20	3.32	0.66	3.80	1.92	1.88	1.02	1.54
41-499	6.79	2.55	4.24	0.60	5.06	2.40	2.66	0.90	1.50
40-268	5.35	2.92	2.43	1.20	3.41	2.25	1.16	1.94	1.62
41-455	5.79	2.67	3.12	0.85	3.70	2.16	1.54	1.40	1.65
41-569	5.72	2.50	3.22	0.78	5.54	3.75	1.79	2.09	2.70
41-551	5.09	2.25	2.84	0.79	9.65	5.10	4.55	1.12	1.42
41-456	6.22	3.02	3.20	0.94	4.46	2.69	1.77	1.52	1.62
40-156	5.68	2.55	3.13	0.81	2.34	1.33	1.01	1.32	1.63
41-527	5.38	3.24	2.14	1.52	3.62	2.60	1.02	2.55	1.68
41-530	6.10	3.19	2.91	1.10	3.42	2.21	1.21	1.66	1.51
41-556	5.31	3.42	1.89	1.81	3.18	2.23	0.95	2.35	1.30
41-557	5.49	3.06	2.43	1.26	3.34	2.03	1.31	1.55	1.23
41-478	5.83	3.23	2.60	1.24	3.57	2.44	1.13	2.16	1.74
40-202	6.86	4.19	2.67	1.57	4.62	3.19	1.43	2.23	1.42
40-388	6.56	2.92	3.64	0.80	3.72	2.10	1.62	1.30	1.63
41-67	5.15	2.40	2.75	0.87	2.69	1.69	1.00	1.69	1.94
Average					4.32				1.69

TABLE IV

SHOCK PRODUCED BY INTESTINAL TRAUMA

PERITONEAL FLUID	TOTAL PROTEIN (GM. %)	ALBUMIN (GM. %)	GLOBULIN (GM. %)	
2 Hr. post-trauma	4.62	3.19	1.43	Control shock
7 Hr. post-trauma	5.30	2.27	3.03	
2 Hr. post-trauma	5.10	3.68	1.42	Shock treated with plasma
7 Hr. post-trauma	5.34	4.11	1.23	

results with the albumin-globulin ratio of burn vesicle fluid (Table V) which also contains more albumin than the corresponding circulating plasma.

The protein content of the bowel and mesentery of ten normal dogs was determined as described under Methods. The results are shown in Table VI and, although there is considerable variation, only one dog (No. 41-451) showed an excessive discrepancy. The average bowel protein content was 4.15 Gm. per kilogram of body weight, or 0.188 Gm. per centimeter of bowel. The bowel protein calculated in terms of bowel length was most uniform and this figure has been used in determining protein balance tables.

TABLE V

BLOOD PLASMA AND VESICLE FLUID IN BURNS

PLASMA				VESICLE FLUID			
T.P.	ALB.	GLOB.	A.-G.	T.P.	ALB.	GLOB.	A.-G.
5.99	3.92	2.07	1.4	3.46	2.78	0.68	4.1
5.62	3.42	2.20	1.5	2.94	2.69	0.25	10.7
5.94	3.19	2.75	1.16	4.64	3.34	1.30	2.6

TABLE VI

PROTEIN CONTENT OF SMALL BOWEL AND MESENTERY IN NORMAL DOGS

DOG NO.	WEIGHT OF DOG (KG.)	T.P. BOWEL (GM.)	BOWEL PROTEIN (PER KG.)	LENGTH OF BOWEL (CM.)	BOWEL PROTEIN (PER CM.)
41-451	13.9	81.0	5.8	285	0.284
41-453	8.2	46.6	5.7	245	0.190
41-397	7.4	34.1	4.6	210	0.162
41-496	8.9	38.8	4.4	250	0.155
41-665	20.5	54.4	2.6	275	0.198
41-634	9.7	44.4	4.6	300	0.148
41-614	11.4	53.9	4.7	240	0.224
41-814	15.0	28.4	1.9	175	0.162
41-805	12.1	43.9	3.6	265	0.166
41-600	13.3	47.8	3.6	255	0.188
Average		49.0	4.15		0.188

The protein content of the traumatized bowel and mesentery at the time of death from shock is recorded in Table VII. There is a uniform increase over that of the normal bowel; the average total protein content was 62.9 Gm., compared with 49 Gm. in the normal. The traumatized bowel contained 4.76 Gm. of protein per kilogram of body weight and 0.216 Gm. per centimeter of bowel. The injured bowel contained less protein than the normal in only three instances.

Fluid and protein balances of the shock experiments are summarized in Tables VIII and IX. The decrease in plasma volume was calculated from the actual circulating plasma volume determined before and during the period of shock. The fluid recovered is the sum of that recovered from the bowel surface, the blood samples (plasma), and the increase

TABLE VII

SHOCK PRODUCED BY INTESTINAL TRAUMA; PROTEIN CONTENT OF TRAUMATIZED BOWEL

DOG NO.	WEIGHT OF DOG (KG.)	TOTAL PROTEIN BOWEL	BOWEL PROTEIN (KG.)	LENGTH OF BOWEL (CM.)	BOWEL PROTEIN (PER CM.)
41-285	12.5			330	
41-383	14.9	62.7	4.2	330	0.190
41-369	12.0	87.7	7.3	300	0.292
41-423	15.7	64.4	4.1	293	0.219
41-416	13.9	109.9	7.9	360	0.305
41-446	14.8	53.5	3.6	315	0.170
41-483	9.5	49.3	5.2	285	0.191
41-511	12.6	64.6	5.1	300	0.215
41-513	8.8	60.3	6.8	285	0.211
41-499	9.3	43.6	4.7	270	0.162
40-268	10.0	55.9	5.6	233	0.240
41-455	17.7	76.9	4.3	360	0.213
41-569	12.6	66.3	5.3	300	0.221
41-551	11.8	61.8	5.2	235	0.252
41-456	16.5	57.9	3.5	308	0.188
40-156	11.9	36.0	3.0	250	0.144
41-527	14.6	83.5	5.7	270	0.309
41-530	14.8	55.0	3.7	270	0.204
41-556	10.0	27.3	2.7	210	0.124
41-557	11.2	46.0	4.1	264	0.174
41-455	12.1	51.3	4.2	265	0.194
41-478	19.3	88.6	4.6	315	0.282
41-796	17.4	59.7	3.4	285	0.209
41-864	16.0	85.5	5.3	310	0.276
Average		62.9	4.76		0.216

TABLE VIII

SHOCK PRODUCED BY INTESTINAL TRAUMA; FLUID BALANCE IN UNTREATED ANIMALS

CIRCULATING PLASMA VOLUME					FLUID RECOVERED				
DOG NO.	CONTROL	SHOCK	DECREASE	FLUID RECOVERED	PERITONEAL FLUID	BLOOD SAMPLES	BOWEL WALL	POSITIVE BALANCE	NEGATIVE BALANCE
41-285	748	335	413	466	300	40	126		53
41-369	868	442	426	294	150	30	114	132	
41-423	710	315	395	515	380	23	112		120
41-416	856	337	519	479	310	32	137	40	
41-446	699	522	177	542	402	25	115		365
41-483	490	352	138	268	125	35	108		130
41-513	560	280	280	293	150	35	108		13
41-499	385	318	67	253	110	40	103		186
40-268	401	238	163	404	280	35	89		241
41-455	868	449	419	612	445	30	137		193
41-551	457	217	240	324	210	25	89		84
41-456	666	389	277	192	50	25	117	85	
40-156	894	319	575	420	285	40	95	155	
41-527	714	339	375	343	200	40	103	32	
41-530	643	252	391	332	196	33	103	59	
41-556	483	254	229	257	145	32	80		28
41-455	642	371	271	243	115	28	100	28	
41-478	773	677	96	430	300	15	115		334
41-796	880	483	397	478	325	45	108		81
41-864	802	557	245	422	260	44	118		177

TABLE IX

SHOCK PRODUCED BY INTESTINAL TRAUMA; PROTEIN BALANCE IN UNTREATED ANIMALS

DOG NO.	DECREASE IN CIRCULATING TOTAL PROTEIN (GM.)	PROTEIN RECOVERED FROM			PROTEIN BALANCE	
		PERITONEAL FLUID (GM.)	BOWEL (GM.)	BLOOD SAMPLE (GM.)	NEGATIVE	POSITIVE
41-369	26.4	8.80	8.4	1.65		7.55
41-423	15.4	10.16	12.85	1.26	8.87	
41-416	29.1	11.43	42.2	1.65	26.18	
41-446	13.7	13.65	5.7	1.48	7.13	
41-483	8.0	8.62	4.3	2.12	7.04	
41-513	18.2	5.7	6.7	2.06		3.74
41-499	8.5	6.01	0	2.31		0.18
40-268	12.6	9.58	12.1	2.06	11.14	
41-455	25.2	17.0	9.2	1.65	2.65	
41-551	13.7	22.2	17.62	1.5	27.62	
41-456	17.9	2.23	0	1.5		14.17
40-156	33.4	6.68	11.0	2.2		13.52
41-527	23.8	7.24	32.74	2.2	18.38	
41-530	26.1	6.70	4.24	1.81		13.35
41-556	13.7	4.6	0	1.76		7.34
41-455	16.4	5.3	1.6	1.54		7.96
41-478	14.7	10.7	29.58	0.79	26.37	
41-796	25.4	11.4	6.1	2.42		5.43
41-864	11.4	9.13	27.0	2.42	27.15	
Total					162.53	73.24

in the bowel weight. The normal bowel weighed an average of 25.6 Gm. per kilogram of body weight, and the traumatized bowel 36.1 Gm. per kilogram. Thirteen of the twenty dogs showed a negative fluid balance, i.e., more fluid was collected in the bowel than was lost in the circulating plasma. Seven dogs had a positive fluid balance. The average loss of fluid in the former group was greater than the retention in those having a positive balance. The possibility of error in these calculations is very great, but they indicate that in general the fluid lost from the circulation can be recovered at the site of trauma.

The protein balance (Table IX) is recorded in the same manner as the fluid balance. Ten dogs had a negative, and nine a positive, balance. The animals that lost more protein at the site of trauma than from the circulating plasma showed a greater protein imbalance than the others. The largest amount of protein lost in excess of the calculated decrease in plasma protein was 27.62 Gm. The largest amount of protein retained was 14.17 Gm.

Tables X and XI are summaries of fluid and protein balances in typical shock experiments when the animals were treated by intravenous injection of plasma in varying dilutions.[4] In the fluid balance the total plasma available is the sum of the initial plasma volume and the volume of plasma injected. The fluid collected is determined in the same manner as previously described. The protein balance was obtained in the same manner. The animals treated with one-half dilution plasma (equal parts plasma and saline solution) had a very small retention of fluid and

TABLE X

SHOCK PRODUCED BY INTESTINAL TRAUMA; FLUID BALANCE IN TREATED ANIMALS

DOG NO.	INITIAL PLASMA VOL (C.C.)	PLASMA INJECTED I.V. (C.C.)	TOTAL PLASMA AVAILABLE (C.C.)	FINAL PLASMA VOLUME (C.C.)	VOLUME PERITONEAL FLUID (C.C.)	BOWEL FLUID AND BLOOD SAMPLES	TOTAL FLUID ACCOUNTED FOR	BALANCE	REMARKS
40-324	650	600	1250	555	410	150	1115	135	Dilute plasma
40-202	805	600	1405	950	400	150	1500	95	Dilute plasma
40-180	1128	350	1478	502	300	140	942	536	Whole Plasma
40-294	908	1060	1968	618	370	150	1138	830	Whole plasma
40-447	738	65	803	435	470	165	1070	267	4× Conc. plasma

TABLE XI

SHOCK PRODUCED BY INTESTINAL TRAUMA; PROTEIN BALANCE IN TREATED ANIMALS

DOG NO.	INITIAL TOTAL CIRCULATING PROTEIN (GM.)	PROTEIN INJECTED (GM.)	TOTAL PROTEIN (GM.)	FINAL TOTAL CIRCULATING PROTEIN (GM.)	PERITONEAL FLUID PROTEIN (GM.)	BOWEL AND BLOOD SAMPLES	TOTAL	BALANCE
40-324	36.2	16.5	52.7	24.4	9.3	12.75	46.45	6.25
40-202	55.2	16.5	71.7	48.2	18.4	12.75	79.35	7.65
40-180	77.2	12.25	89.45	26.0	14.37	12.0	52.37	37.08
40-271	62.7	55.0	117.7	35.4	20.8	12.75	68.95	48.75
40-447	40.0	25.0	65.0	21.0	24.0	12.47	57.47	17.53

protein. These animals also showed the best response to treatment. The dogs treated with large amounts of whole plasma and four times concentrated plasma retained large amounts of fluid and protein. These dogs did not respond as well to treatment. A large amount of the plasma which disappeared from the circulation could not be accounted for at the site of trauma.

DISCUSSION

The arterial blood pressure is not always a satisfactory criterion by which the severity of the shock state may be evaluated in the experimental animals. The arterial tension may be maintained at a near normal level for many hours during which the animal has a marked increase in the hematocrit and a reduced circulating plasma volume. In such an animal the pressure is often maintained until immediately before death and then may fall precipitously. Experience gained from these experiments again accentuates the impression that the development of shock requires a period of time, and that regardless of the blood pressure a progressive chain of events is instigated by the trauma. The maintenance of the pressure in some animals is probably due to narrowing of the circulatory bed by peripheral vasoconstriction until the

vasomotor center fails and the circulation collapses. This same reaction may be repeatedly observed when dealing with patients, and the fallibility of the blood pressure as a sign of shock has been emphasized.

The changes in the circulating protein during the development of shock are very definite. The concentration of circulating total protein, and thus the plasma specific gravity, decrease. This can be due to one of two factors, either dilution of the plasma with interstitial fluid or a loss of plasma from the circulation. The actual mechanism is probably very complex and involves both factors. It is evident that a large amount of fluid and protein are lost at the site of trauma, but since this fluid contains less protein than plasma there must be some dilution of remaining plasma by reserve body water.

The albumin-globulin ratio of the peritoneal fluid is always greater than the circulating plasma. This indicates a greater proportional loss of albumin than globulin, and corresponds to the loss of protein in the vesicle fluid of burns and in shock produced by peritoneal cooling.[5] Also in these experiments an increasing amount of globulin is present in the peritoneal fluid when the animal is approaching death. A plausible explanation is that with some increased capillary permeability early in shock the smaller albumin molecule is able to escape. As shock progresses the permeability increases and the larger globulin molecule can also pass through the capillary wall. In these experiments the increased capillary permeability occurs at the site of trauma, but a general change in the capillaries can in no way be excluded.

The amount of fluid and protein which is lost from these animals is the sum of that fluid which oozes from the serous surface of the bowel and that amount which is present in the bowel wall and adjacent mesentery. The fluid which escapes can be measured accurately as to volume and protein content. That portion in the bowel and mesentery is determined by relative comparison of normal and traumatized bowel weight and protein, deducting a correction for hemoglobin. There may well be a considerable possibility of error in using an average figure for normal bowel protein, but the value used does approximate the mean of that found in all control animals. The bowel protein content of the animals in shock was consistently greater than that of the controls. In ten animals more protein was recovered at the site of trauma than could be calculated as lost from the circulating plasma. Less protein was recovered at the site of trauma in nine dogs. If all the protein is lost at the site of trauma one would expect to recover the total which disappears from the circulation. In many experiments considerably more protein is recovered. The possible origin of this is from a mobilization of reserve protein stores. This does not agree with Ebert and his co-workers[3] who feel that protein stores cannot be mobilized following shock from hemorrhage.

In the nine dogs in which all the protein could not be recovered only three showed a significant retention. The results in these nineteen dogs

tend to indicate that in most of the animals the protein lost from the circulation can be accounted for at the site of trauma. There is a similar tendency for all of the fluid lost to be found in the same area (Table VII). It must be emphasized that this occurs in a specific type of shock (intestinal trauma) and these results do not necessarily apply to shock from other causes.

It is very difficult to interpret the significance of the fluid and protein balance records in this type of shock when treated with varying dilutions of plasma. The total amount of plasma injected could not be accounted for in any of the experiments. The most satisfactory therapeutic results were obtained in the animals treated with dilute plasma (equal parts plasma and saline solution). In these experiments the fluid and protein balance was most nearly equal. In other experiments, using large amounts of whole and four times concentrated plasma, a large amount of fluid and protein did not appear at the site of trauma. Less satisfactory therapeutic results were obtained in these animals. The loss of fluid and protein could be explained by a trapping in the circulatory bed or extravasation from the circulation because of a generalized increase in capillary permeability. It is of interest that the liver, spleen, kidneys, and lungs of these animals showed the minimum congestion previously described in control animals.[4]

There has been no opportunity as yet to attempt to determine the fate of the lost plasma. A comparison of the wet and dry weights of organs of normal and shocked animals has not been helpful. At most, a very small amount of this protein appears in the urine. A very small amount of urine is excreted during the experiments and this rarely contains albumin.

SUMMARY

The results of these experiments indicate that progressive capillary damage results from the trauma to the bowel wall and this allows fluid containing protein to pass through the wall. In the first stages the smaller albumin molecule readily passes through the capillary wall, but as shock progresses the permeability increases. During the later and terminal stages the globulin passes out of the capillaries in increasing amounts. In these experiments this change in capillary permeability probably occurs primarily at the site of trauma. In balance studies on untreated shock of this type it is not necessary to postulate fluid and protein losses other than at the focus of injury. That a generalized capillary permeability can develop is indicated by the large amount of unrecovered fluid in the animals treated with plasma.

CONCLUSIONS

1. Fluid and protein shifts have been studied in experimental shock produced by intestinal trauma.

2. The plasma specific gravity and protein concentration decrease as the shock progresses.

3. The albumin-globulin ratio of the fluid recovered at the site of trauma is greater than that of the circulating plasma.

4. More albumin is lost in the early phase of shock; more globulin in the terminal phase.

5. The major proportion of fluid and protein lost from the circulation can be recovered at the site of trauma when the shock is not treated. This is not true when the shock is treated with plasma.

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PROLONGED DEPENDENT DRAINAGE WITH "LUCITE" DRAINS IN THE TREATMENT OF CHRONIC OSTEOMYELITIS*

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ONE hundred thirty-three cases of hematogenous osteomyelitis have been seen at the University of Minnesota Hospitals in the past five years.[2] Forty-four of these were seen and treated at this clinic in the acute stage, and the only therapy which thus far has resulted in healing directly from the acute stage is oral sulfathiazole administration, with or without local implantation as well.[4] The great majority of the cases became chronic, and therapy in this stage of the disease has been widely varied. The use of maggots, as introduced by Baer, and of the Carrel-Dakin technique have not been tried in recent years here. On the orthopedic and general surgical services, between which these cases are divided, the Orr treatment has been used in a small number of cases, with successful wound healing in more than half. The policy for several years was expectant in character, without intervention unless abscess formation, pain, or sequestrum formation appeared.[10] Healing with cessation of drainage under this regimen occurred in only one-quarter of the cases.

Despite the moderate number of lesions which have ceased to drain or cause pain or fever, the impression remains that no standard method of treatment of chronic osteomyelitis has been demonstrated to lead to healing of a permanent nature. The patient in case after case has returned with an exacerbation months or even years after apparently complete healing had occurred.

Examination of the roentgenograms of bones of patients treated in the manners described reveals, even in the period of quiescence, areas of rarefaction highly suggestive of bone abscesses, areas of gross irregularity, and areas of markedly increased radiopacity (Fig. 1). Such pictures imply quiescence rather than a true return to normal function and architecture.

The Choice of Drainage Material.—Because of this failure in the handling of the chronic disease, Wangensteen suggested three and one-half years ago that a trial be given to prolonged dependent drainage and also that a tubular drain of some such nature as the glass abdominal drains formerly used in some European clinics be given a trial.

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It was decided to test the tolerance of tissues to various substances which might be used as drains. Pieces of tubular and sponge rubber were implanted into the thigh muscles of three dogs. Uniformly, suppuration occurred and one of the animals died of this cause. Glass was not tried because of fear of breakage if used in clinical cases. In a search for some unbreakable glass, a composition, "lucite"* was found. After remaining for four weeks in apposition to an implanted piece of this material, the muscle of a dog's thigh showed no gross or microscopic evidence of inflammatory reaction. A narrow border of fibrosis (1.5 mm.) surrounded the foreign body, and a layer of flattened cells suggesting endothelium lay on the surface of the tissue (Fig. 2). From ten days after implantation of this material the dog showed no evidence of local tenderness or heat. It was therefore decided to use lucite in a few clinical cases.

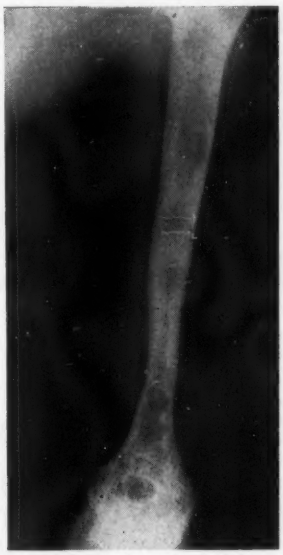


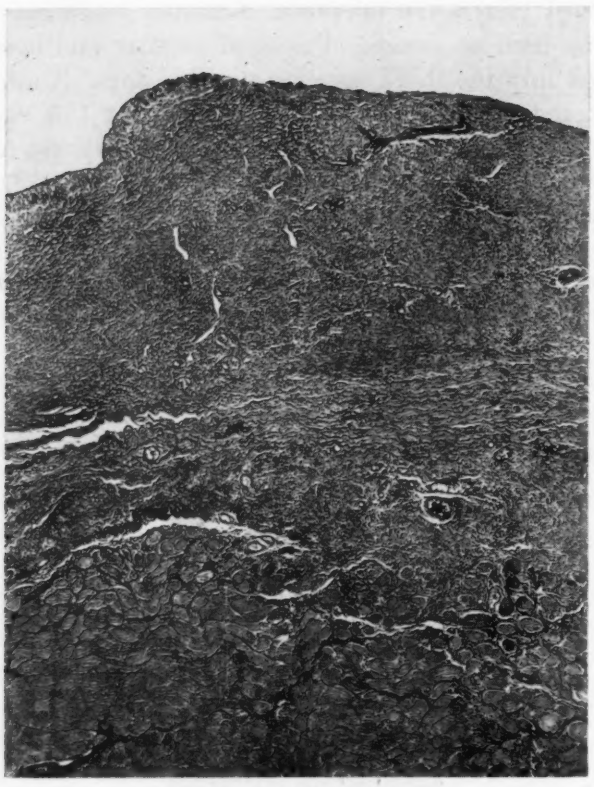
Fig. 1.—Roentgenogram of a humerus in the quiescent stage of chronic osteomyelitis. There is no drainage, but the patient has pain at times. Note the areas of rarefaction and the areas of increased density.

This material proved particularly useful for the purpose in mind, for it can be molded and bent at will when immersed in boiling water, and it is difficult, though not impossible, to break.

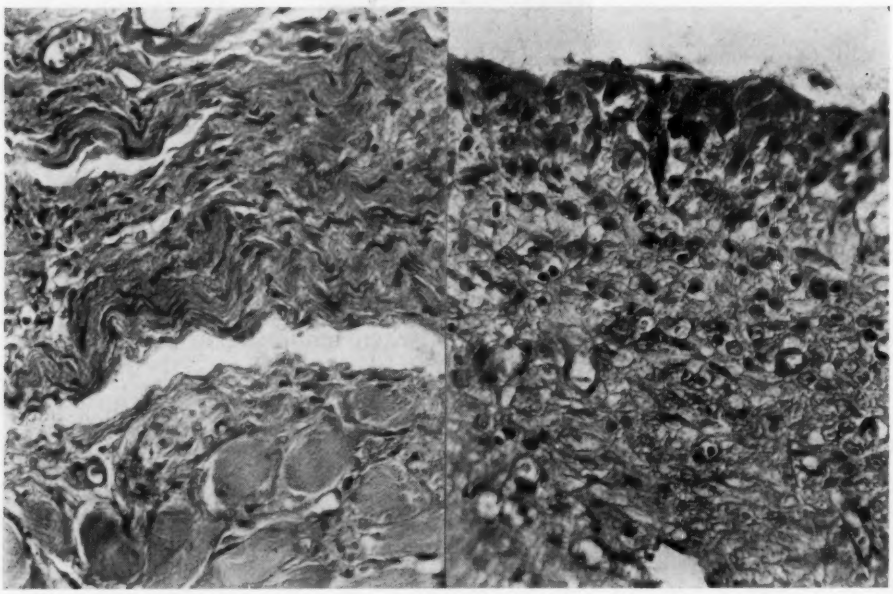
Vitallium was considered as a nonirritating material, and has been reconsidered since Pearse has used it successfully in other locations than bone and has shown that there is very little tissue reaction to it in the common bile duct. It was not used in the present instance for the reason that it cannot be worked at the operating table to suit the individual case.

The Configuration of the Drains.—In order to provide an adequate drainage tract, one that should prevent the accumulation of pus and

*Manufactured by E. I. du Pont de Nemours Co., Arlington, N. Y.



A.



B. *C.*

Fig. 2.—Reaction of the muscle of a dog adjacent to a piece of lucite left in the tissues for one month. *A*, Layer of fibrosis, rather well vascularized, between site of the plastic material and the muscle layer (magnification ×40). *B*, Junction of the area of fibrosis and muscle, showing fibroblasts, but no inflammatory reaction (magnification ×200). *C*, Surface of the tissue adjacent to the lucite; on the surface are cells suggesting endothelium (magnification ×200).

debris, tubular drains were fashioned. Rather small ones were used early, but they tended to become plugged, and the standard size now is 1 cm. in external diameter, 7 mm. in internal diameter, and of a variety of lengths, with a flange 18 mm. in diameter and 3 mm. thick at one end. Holes were drilled in the flange for fixation (Fig. 3).

Sterilization caused some difficulty at first. The material loses shape if boiled, and phenol and alcohol render the surface rough and gummy. Aqueous metaphen solution proved to be satisfactory.

The Placement of the Drains.—The most satisfactory use of these drains has been found in osteomyelitis of the tibia, in which it seemed possible to maintain dependent drainage regardless of whether the patient was recumbent or upright. In the first case in which the method was tried, the drains were inserted as illustrated in Fig. 3, and subsequent cases have differed from this only in minor details.

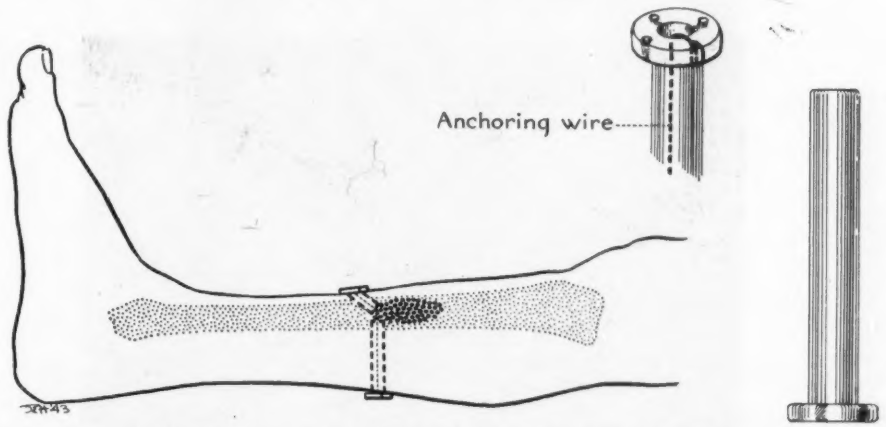


Fig. 3.—The lucite drain. It is 1 cm. in external diameter and 7 mm. internally; it is of varying lengths. There is a flange 18 mm. in diameter at one end, in which holes are drilled. The drains are inserted in such fashion as to allow dependent drainage of osteomyelitic cavities regardless of whether the patient is in the recumbent or the upright position. The flange of the anterior drain is bent to be parallel with the skin. A stainless steel wire passes through both drains and the leg, and is anchored to each flange.

To accomplish proper placement in the tibia, the skin and soft tissues over the anterior surface of that bone were incised, the bone was opened anteriorly into the pocket, and most of the bony roof of the cavity was removed. At the caudal end of the cavity, a $^{13}/_{32}$ inch drill was used to penetrate the bone straight back, and the graduated-diameter trocars of Wangensteen's set for drainage of lung abscess[11] were pushed through the soft tissues and skin posteriorly until a large enough trocar had been reached to permit placement of a lucite drain from behind. It was quickly learned that the head of the drain must lie about 4 mm. away from the skin at first, to prevent pressure irritation from postoperative swelling of the calf muscles. The anterior drain site was exposed by excision of a disc of skin and soft tissue 1 cm. in diameter and a hole for the drain was drilled upward and backward at an angle of about 45 degrees. The head of the anterior drain was placed in hot

water and bent to lie parallel with the skin on insertion. The bone cavity was loosely packed with dry gauze, which was withdrawn during the next few days.

After a trial of a number of methods of securing these drains in place, the use of stainless steel or silver wire was adopted. It is regularly passed through the lumina of both drains, and thus through the extremity, and is anchored to the flange of each drain (Fig. 3). Burial of each end of the wire in one of the holes of the flange prevents catching of the dressings on the ends.

Use of the Drains in Management of Chronic Osteomyelitis.—In each case a plaster cast was applied, leaving a wide margin to facilitate change of dressings without contamination (Fig. 4). As soon as healing of the soft tissues had occurred, i.e., in about two weeks, the plaster was removed, and full activity was allowed.

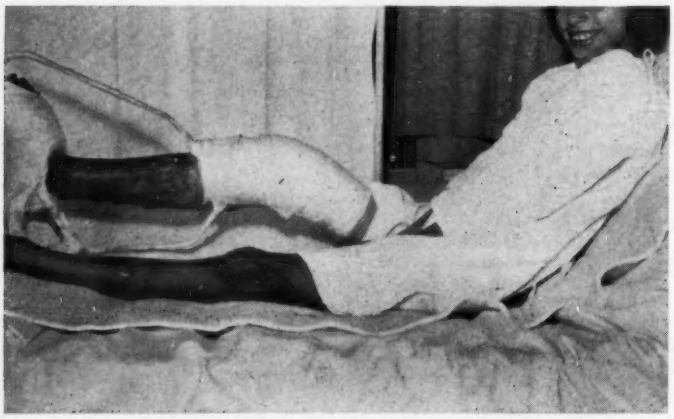


Fig. 4.—The manner of placement of plaster casts for two weeks after insertion of lucite drains. Ample margin is allowed to avoid contamination during irrigations and dressings. There is very little discomfort.

Daily irrigation with Dakin's solution was employed to keep the drains open in most of the cases.

The first patient treated in this manner was a boy of 12 years of age who had had osteomyelitis of the tibia for nine months. The lesion showed little prospect of healing, and a large pocket was visible on roentgen examination in the upper end of the bone (Fig. 5). On Feb. 8, 1940, lucite drains were placed as already described. Subsequent roentgenograms indicated a gradual healing of the pocket, apparently by regeneration of bone (Fig. 6). The drains were both shortened six months after insertion, and again at twelve months; the posterior drain and anchoring wire were completely removed at thirteen months; and finally, the anterior drain, which had been held for three months with adhesive plaster and heavy thread was removed at sixteen months. The drainage sites healed within a few days and have remained healed, allowing the boy to play football at school without apparent handicaps.

Roentgenograms in the eighteen months since complete removal of the drains indicate a gradual return toward normal bony architecture (Fig. 7).

Results of prolonged Drainage in a Series of Patients.—Twelve lesions in eleven patients have been treated in this fashion. The essential data are presented in Table I. In general, one or two drains were placed in each bone pocket. Apparently complete healing occurred in four of the lesions, frank failure resulted in two, and five are still under treatment. Three of these latter offer definite promise of ultimate success. In one other case the drains have been removed too recently to allow certainty.*

Fig. 5.—*A*, Roentgenogram showing marked early destruction of the upper tibia, July 17, 1939, eleven days after onset. *B*, Progressive sclerosis with formation of a large pocket in the same patient, Jan. 26, 1940.

One of the failures (Case 6) was in disease of the humerus in a fat muscular girl, 11 years of age, in whom the drains could not satisfactorily be held in place; they probably were not properly inserted in the first place. Healing took place later under experimental chemotherapy by Dr. Wesley Spink. In the other failure the disease involved the lower femur, and the bone was of such poor quality that openings for insertion of the drains were made with the thumb nail. The bone has become strong enough to permit use of the leg and all pain has been relieved, but profuse drainage persists after thirty months, and removal of the drain is not tolerated (Case 3).

A striking relief of the discomfort and ache of chronic osteomyelitis has been observed after proper placement of these plastic drains. In

*Two of these latter cases have healed (5/10/43) since submission of this paper for publication.

TABLE I

COURSE OF CHRONIC OSTEOMYELITIS FOLLOWING USE OF LUCITE DRAINS

PATIENT NO.	AGE OF PATIENT	DURATION OF DISEASE	SITE	NO. OF DRAINS	DURATION OF DRAINAGE	DATE OF REMOVAL	PRESENT STATUS
1. T. M. (683797)	12 yr.	9 mo.	tibia	2	16 mo.	6/ 6/41	Healed 18 mo. (1/1/43)
2. G. J. (669738)	13 yr.	2 yr.	radius	2	1½ mo.	4/ 8/40	Healed 3 mo. (10/16/40)
3. A. H. (684222)	27 yr.	16 yr.	femur	2	30 mo.		Drain in place, not promising
4. M. V. B. (699394)	9 yr.	9 mo.	tibia	7	20 mo.		2 drains in place, still promising
5. E. H. (648299)	32 yr.	23 yr.	tibia	2	15 mo.	8/24/42	Healed 2 mo. (2/1/43)
6. P. M. (695433)	10 yr.	17 mo.	tibia	1	9 mo.	6/26/42	Healed
		21 mo.	humerus	2	10 mo.	11/27/42	Failure; healed by chemotherapy
7. L. E. (653500)	11 yr.	5 yr.	tibia	4	13 mo.		2 drains in place
8. F. C. (714164)	31 yr.	18 yr.	tibia	2	9½ mo.	8/31/42	Healing (?)
9. E. F. (698881)	22 yr.	18 yr.	tibia	2	12 mo.		Drains in place
10. A. V. (717558)	30 yr.	16 yr.	femur	9	11 mo.		Drains in place
11. G. B. (723367)	20 yr.	2 mo.(?)	tibia	2	6 mo.		Drains in place

Fig. 6.

A. *B.*

A. *B.*

Fig. 7.

Fig. 6.—*A*, Roentgenograms of the same patient, April 16, 1940, two months after insertion of the drains. Casts were not usually used this long. *B*, Diminution in sclerosis and beginning healing of the bone cavity, Jan. 2, 1941.

Fig. 7.—*A*, Roentgenogram showing continued diminution in sclerosis, and partial healing of the drainage tract on July 31, 1941, two months after removal of the drains. *B*, Plate of same bone as Figs. 5 and 6 showing appearance on Aug. 26, 1942, fifteen months after removal of the drains. The appearance of the bone has returned almost to normal.

most of the cases, return to normal activity has been demanded by the patient, and no ill effect from this has been recognized (Fig. 8). The patient who now wears nine drains in his femur had been bedridden for a year despite numerous conventional procedures for his disease. After placement of the drains, he walked about the house within two months, and is achieving gradually increasing activity.

In Table I, the patient in Case 2 had sodium sulfathiazole irrigations for three days through the drains, and the patient in Case 10 had local implantation of 8 Gm. of free sulfathiazole at the time of placement of the drains. Aside from these two, no local chemotherapeutic agent except Dakin's solution has been employed, the aim being to evaluate continued drainage before the admixture of other measures.

Fig. 8.—A patient who has worn drains for a year, and has had some of them removed. Most patients demand full activity within a few weeks after insertion of lucite drains.

COMMENT

Lucite, being relatively little irritating to the tissues, has been implanted elsewhere in the body. W. T. Peyton, of this clinic, has implanted a lucite orbital roof in a patient at my suggestion, and the plate is still in place after over six uneventful months. Serious consideration is being given to the preparation of larger plates to use in covering defects in the skull. Such plastic plates would have an advantage over vitallium because of the pliability of the material under hot water.

Lucite is also being used in experimental work by K. A. A. Merendino, in the laboratory, where it has been found most useful to make cannulae of practical design for gastric pouches during further study of the ulcer problem.

At the present time, tubes of the type described by Pearse are being placed in the common bile ducts of dogs in order to determine the degree of reaction to them.

With regard to the problem of osteomyelitis, the importance of continuous drainage is thought to rest in the quick evacuation of pus and also in the prevention of local pressure elevation, even though use of a manometer and a hollow drill inserted into foci of recurrent osteomyelitis has failed on two occasions to demonstrate such a rise. This contention is supported by the marked relief of discomfort which is afforded by placement of drains.

The proper time period during which drains should remain in place has not been settled. In Case 8, they were apparently removed too early, and healing after removal does not seem too certain to occur. For the larger bones, it appears at present wisest to shorten or remove drains only when roentgen evidence indicates healing to the end of the drain. In the tibia, this has meant about fifteen months of drainage.

The management of chronic osteomyelitis has been materially altered by the brilliant reports of Spink and Paine, followed later by Dickson, Dively, and Kiene, and by Key. They observed healing in a high percentage of cases following saucerization, sulfathiazole implantation, and primary closure. At the University of Minnesota Hospitals healing has occurred seven times in twelve trials of this method, and in two other cases healing still seems likely to occur. These patients in whom healing has taken place are not immune to occasional bouts of recurrent pain, and their roentgen pictures indicate the persistence of abnormal bony architecture. In my opinion, therefore, long-continued dependent drainage is the form of treatment which best restores normal bony architecture and therefore may best be expected to achieve a permanent cure.

Utilization of this method of therapy seems best adapted to superficial long bones, particularly the tibia. This is the bone in which saucerization, sulfathiazole implantation, and primary closure are most difficult because of the inadequacy of soft tissues for obliteration of the resulting dead space. It is likely that judicious choice between the two methods in specific cases will offer the best over-all results.

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RADICAL OPERATION FOR INTRACTABLE PRURITUS ANI

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PRURITUS ani is a symptom complex rather than a definite disease, characterized by intense itching about the anus. The itching is aggravated by warmth and hence is often most troublesome at night.

There probably is no single cause of this symptom. In adults it is most often associated with moist perianal skin. The moisture in women may be due to chronic vaginal discharge, and in both men and women to irritative rectal lesions such as fissure or hemorrhoids. Moist perianal skin is more common in obese individuals, due to constant apposition of the buttocks. In some patients infrequent bathing may be a contributory factor. The symptom is frequent in diabetics.

In most instances of long continued pruritus ani, the perianal skin becomes pigmented, leathery, thickened, and often excoriated by scratching. These changes may be due to a disease entity, but more probably are the end results of repeated injury from scratching. A microscopic examination of this scarred pigmented perianal skin shows nothing other than increased deposits of pigment and chronic inflammation.

In many instances the symptoms may be relieved by the correction of local anal lesions; in others, by scrupulous cleanliness and the use of drying ointments or powders. In all cases these general causes should be looked for and, if present, treated.

In more refractory cases subcutaneous alcohol injections have been used to destroy nerve endings in the perianal area. This treatment is based on the same rationale as the older surgical procedure of undercutting the perianal skin and subcutaneous tissues and then suturing the flaps so raised in their original beds.

We are all familiar with the above facts but we are also well aware that there are occasional stubborn cases of pruritus ani which are not relieved by any of these measures. Hence, any method of treatment which affords relief from the intractable itching occasionally encountered should receive attention.

It should not be inferred that the radical method reported here should be used in all, or even an appreciable percentage, of cases of pruritus ani but in the occasional instance where symptoms are severe and cannot be relieved by ordinary methods. The following report is of such a case.

Presented at the meeting of the Society of University Surgeons, Chicago, Ill., Feb. 11-13, 1943.

CASE REPORT

M. S. (S.M.H. No. 146602), a white physician's wife, aged 51 years, entered the Strong Memorial Hospital on Jan. 3, 1939. She complained of pruritus vulvae. This symptom, at times more troublesome than at others, had been experienced for the past twenty years. In the past one or two years it had become more severe and the itching had extended to the perianal region. Leucorrheal discharge, which had always been present, had become quite marked in the past year. This did not seem to have aggravated the itching. Her last menstrual period had been in January, 1938. During the two years prior to entry she had been treated with both radium and x-ray radiation over the vulvar and anal regions. The exact dosage was unknown, but there had been no relief of symptoms. During the three months before hospital admission she had received 10,000 units of progynon a week, for six weeks, without improvement. During the month before admission she had been given 10,000 units of progesterone twice a week. This had given slight relief from itching.

A detailed history revealed nothing of importance in the past, other than that she had always been in good health. A cholecystectomy and appendectomy had been done twelve years previously.

General physical examination showed no abnormal findings. The labia majora and minora were hypertrophied, thickened, red, and scaly. This abnormal condition extended up to the mons and downward around the anus. Rectal examination showed hemorrhoids present externally.

Laboratory findings were Hb., 14.5 Gm.; R.B.C., 4,750,000; W.B.C., 6,000; blood N.P.N., 35 mg. per cent; blood sugar, 145 mg. per cent; urine, negative; Wassermann, negative.

The diagnosis made on the gynecological service where she was first admitted was kraurosis vulvae and pruritus vulvae.

On Jan. 4, 1939, a radical vulvectomy, a dilatation and curettage, and a cauterization of the cervix was done on the gynecological service. At the same time the external hemorrhoids were removed. She had a satisfactory convalescence and was discharged on Jan. 28, 1939, with the vulvar incisions healed.

This operation relieved her entirely of pruritus vulvae but not of pruritus ani. On March 28, 1939, we were asked to see her because of the intense anal itching. At that time there was an area from the vaginal orifice to the tip of the coccyx and extending laterally about the anus for about two inches which was thickened, red, and leathery, with some white plaques interspersed through the red area. Since vulvectomy there had been no leucorrhea and an attempt had been made to control the itching by keeping the skin dry with borated alcohol. This had not been at all effective in controlling the itching.

She was advised to have the involved perianal skin excised. She entered the hospital again and on April 25, 1939, the right half of the pruritic area was excised and the defect covered with a flap. During the postoperative period the main problem was one of keeping the area dry. She was kept on her stomach to prevent vaginal discharge and urine from running down over the wound. The bowels were allowed to move on the ninth postoperative day. The flap healed in place well and she was discharged on the fourteenth postoperative day. At that time there was a small granulating area laterally from which the flap had been shifted. This healed promptly.

On July 6, 1939, as the right side was symptomless and had been healed for some time, the remaining left hemisphere of scarred perianal tissue was excised and covered with a flap. It was possible on this side to close the defect from which the flap was obtained. These wounds healed nicely so that she could be discharged from the hospital on July 24.

She was last seen on May 16, 1941, a little less than two years after completion of the two-stage operation. At that time she was entirely free from itching. For

about one year after operation she said that she had difficulty sitting for prolonged periods. This was due not to soreness but a feeling about the anus of numbness similar to when one's leg "goes to sleep." At the end of about a year sensation returned to the shifted skin and she no longer had this difficulty. On examination the skin appeared perfectly normal with good sensation. The result was considered excellent.

OPERATIVE TECHNIQUE

Because of the probability of some infection and perhaps consequent poor and prolonged healing, we believe it best to excise only one-half the involved perianal skin at a time. This allows a safety factor, in case infection and scarring might cause contracture of the anal orifice. The procedure in brief is a complete excision of the scarred perianal skin, one hemisphere at a time, and a shift of a flap from the medial surface of the buttock and thigh to replace the excised area. The flap need not be delayed because the blood supply is entirely adequate.

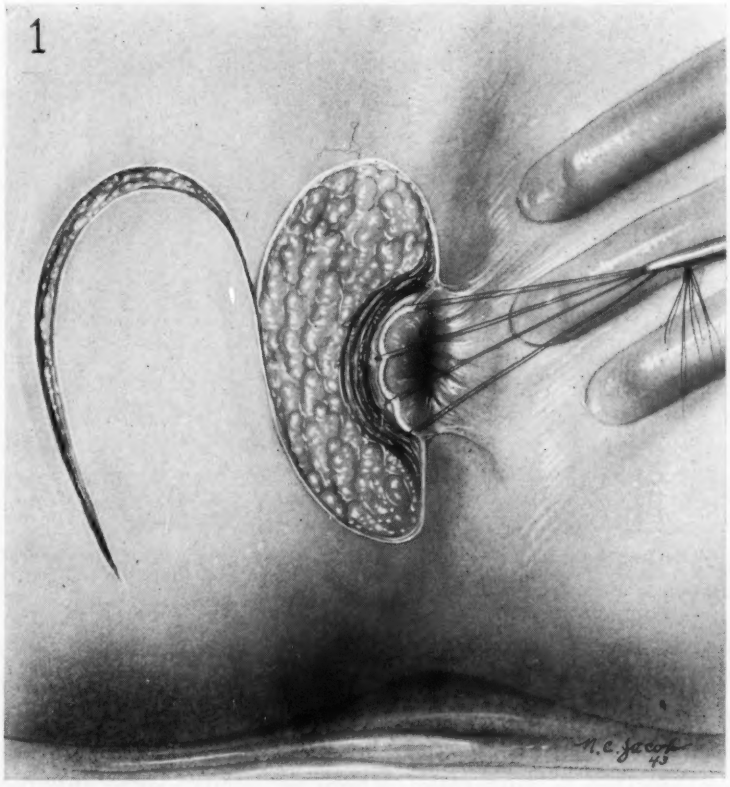

Fig. 1.—Showing the manner in which the flap is cut for resurfacing one-half the perianal area.

An incision is made at the mucocutaneous junction around one-half the circumference of the anus. The mucosal edge is prevented from retracting inward by a number of guy sutures which are held by an assistant. The external sphincter muscle is exposed and the scarred skin and subcutaneous tissues dissected from it. A plane of dissection is

found under the leathery area and the dissection carried outward from normal skin. The flap of scarred tissues is then cut away (Fig. 1). A flap of skin and subcutaneous tissue of correct size and shape to cover the defect is cut lateral to the defect with its base posteriorly. It is swung across and sutured to the anal mucosa and to the medial line of excision (Fig. 2). The defect left laterally is sutured as far as possible. If tension is observed, the remainder of the defect is left to granulate. The operation is done in the lithotomy position and any tension on the flap becomes less

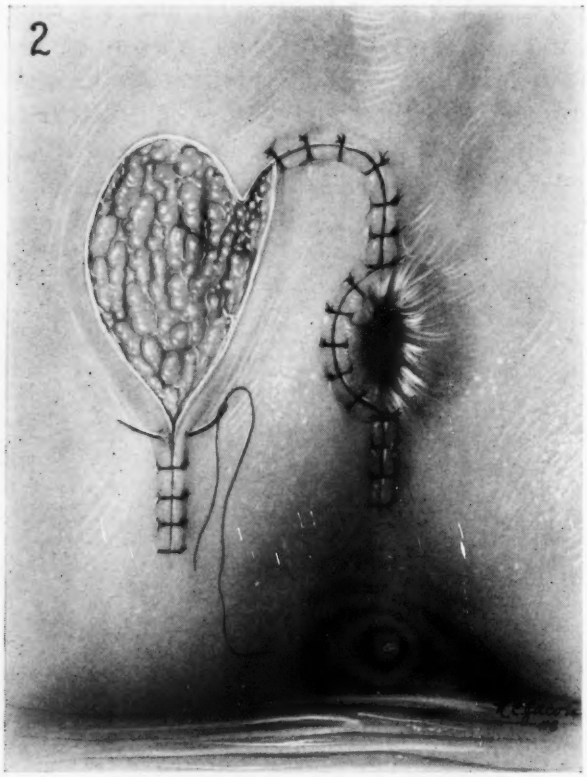

Fig. 2.—The flap has been sutured medially and the closure of the lateral defect begun. It is usually possible to close this incision, but if there is any tension, the superior portion is allowed to granulate.

when the legs are again straight. A small rubber drain is brought out from under the flap at its base and a snug perineal binder is applied to hold the flap securely in apposition to its bed. The bowel is prevented from moving for ten to fourteen days depending upon the speed of healing. Infection is moderate. There is usually some inflammatory reaction along the suture lines but not enough to interfere with healing. In two to three months the remaining half of the prianal skin is removed and replaced in the same manner.

DISCUSSION

We have so far had occasion to operate on three such patients with intractable pruritus ani. Two of these are entirely symptom free for

long enough periods to be thought permanently relieved. The third has had one hemisphere of perianal tissue removed and is about to have the operation completed. As yet he still has marked symptoms on the unoperated side. He also complains of itching on the flap on the operated side although this skin is still anesthetic. Whether this is actual or due to the unoperated side will be determined on completion of the procedure.

It would seem that in a selected group of cases of pruritus ani, where all other measures have proved ineffectual in relieving symptoms, that complete excision of the abnormal perianal tissues, one-half at a time, and replacement with a flap from the buttock and thigh may be effective treatment.

GASTRIC ACIDITY FOLLOWING GASTRIC RESECTION

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DURING the past twenty years gastric resection has become more and more popular as a method of surgical treatment of peptic ulcer. There are two advantages of this procedure over the more conservative operations such as pyloroplasty or gastrojejunostomy. They are, first, that the ulcer is removed and, second, that the gastric acidity may be lowered, thereby reducing the danger of the development of secondary ulcer. It is now realized that small resections usually fail to reduce the acidity and, as a result, larger resections as well as various mutilating procedures on the stomach have been advised in the hope of regularly producing postoperative gastric anacidity.

The purposes of this report are to present a summary of findings on eighty-eight patients upon whom gastric resections have been performed for peptic ulcer and to emphasize certain technical features of resection which make it a practical procedure and one often resulting in a low postoperative acidity.*

There are many surgeons[1-6] who advocate extensive resections of the stomach in the hope of insuring a low postoperative acidity. Their opinion is based upon the generally accepted idea that gastric acidity plays an important part in either the formation or the persistence of an ulcer and that if postoperative anacidity can be obtained, secondary or recurrent ulcer can be prevented. The objections to these extensive resections (more than two-thirds of the stomach) are, first, that it has not been proved to date that they are more effective in reducing acidity than less extensive resections (one-half to two-thirds). Second, when such a large amount of stomach is sacrificed and a recurrent ulcer develops, a secondary procedure is not only difficult but hazardous; and third, except in the hands of an expert, the mortality is too high. With these features in mind, we have attempted to determine the type of resection that most often produces a low postoperative acidity, is relatively safe and simple, and also retains a sufficient amount of stomach in case a secondary operation becomes necessary.

*A detailed analysis of all cases of peptic ulcer operated upon in the New York Hospital is being reported by Heuer et al.[7]

Presented at the meeting of the Society of University Surgeons, Chicago, Ill., Feb. 11-13, 1943.

MATERIAL AND METHODS

This study is based upon the findings of eighty-eight patients who have had gastric resections for peptic ulcer, of which twenty-five were gastric and sixty-three duodenal. The follow-up studies and gastric analyses were performed repeatedly over a period of from one to seven years after operation; however, only 25 per cent were followed for more than five years. All patients were personally interrogated, and rather severe criteria were used as a basis for evaluating results. Likewise all analyses were performed by us and on some patients as many as six gastric analyses were done. All patients listed as having low acid or anacidity had at least two determinations done. Additional patients studied, in whom it was felt that satisfactory tests were not obtained, are not included in this report.

The method used in obtaining specimens of gastric juice is that suggested by Bloomfield and Polland.[9] The examination is made after a fast of twelve hours, with histamine used as a stimulus in a dosage of 0.1 mg. to each 10 kg. of body weight. The fasting contents are withdrawn, the histamine injected subcutaneously, and the stomach contents continuously aspirated with a syringe and collected for three ten-minute periods. The acidity is then titrated against $\frac{1}{10}$ normal sodium hydroxide, Toepfer's reagent and phenolphthalein being used as indicators. The ten-minute specimen with the greatest ten-minute volume of secretion and the highest titratable acidity obtained is considered the index of gastric function. The importance of following the described procedure in detail in order to obtain an accurate analysis cannot be too greatly stressed.

To insure a precise determination of acid secretion, several requisites must be recognized. First, the person performing the aspiration must be a physician familiar with the technique of gastric aspiration and must be interested in the procedure. The delegation of the test to a nurse or to a technician repeatedly leads to error. It has been our experience on numerous occasions that the results obtained by the relatively uninterested technician will not compare with the results obtained by a doctor who is responsible for and interested in the result obtained. Second, the stomach must be aspirated absolutely dry before the fractional specimens are collected. This procedure frequently takes from ten to fifteen minutes and on occasions the test may have to be abandoned for the day because of the constant regurgitation of bile. Third, dilution of the gastric contents must be avoided; the patient should be required to expectorate all saliva and all bile-tinged specimens should be discarded. The volume of secretion characteristically follows a more or less regular curve and this characteristic can also be used to check the accuracy of the procedure. Fourth, there are obvious difficulties and inaccuracies in these determinations on the postoperative stomach, and for this reason repeated studies must be made on those patients who are found to have low acid or anacidity. Since the error in gastric analyses

results in too low rather than too high a value of secretion, it is not uncommon to discover that a patient in whom a previous anacidity was found, upon repeated test, shows adequate acid.

The normal standard of gastric secretion as obtained by the method just described has been determined by Bloomfield and Polland.[9] In general, it may be said that the normal range of free hydrochloric acid is between 60 and 110 degrees and the maximum ten-minute secretory volume between 15 and 35 c.c.

RESULTS

The types of resection may be divided into three groups: (1) those in which the antrum was removed (Fig. 1, *A*); (2) those in which one-half to two-thirds of the stomach and a portion of the lesser curvature beyond the incisura angularis were removed (Fig. 1, *B*), and (3) those in which more than two-thirds of the stomach was removed (Fig. 1, *C*). Several observers have reported that simple removal of the antrum of the stomach usually fails to reduce the postoperative acidity; our observations confirm these reports (Table I). Our main point of interest was

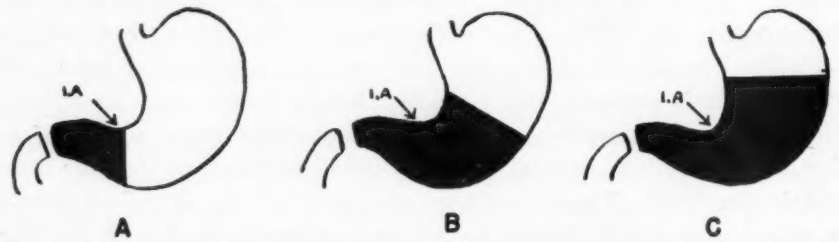

Fig. 1.—Three types of resection which were done upon patients discussed in this report. *A*, Resection of pyloric antrum; *B*, Resection as we suggest, carried proximal to the incisura angularis (*I.A.*) on lesser curvature and leaving a fair portion of the greater curvature; *C*, resection of more than two-thirds of the stomach.

to determine whether removal of one-half to two-thirds of the stomach as shown in Fig. 1, *B* results in as high a percentage of anacidity as does removal of larger portions of the stomach (more than two-thirds, Fig. 1, *C*).

TABLE I

ANTRAL RESECTION

	NUMBER	ANACIDITY	LOW ACIDITY	NORMAL OR ADEQUATE ACIDITY*
Gastric ulcer	6	2	2	2
Duodenal ulcer	25	0	4	21
	31	2 (6%)	6 (19%)	23 (75%)
		25%		

*Free hydrochloric acid of 60 degrees or more was considered normal or adequate acid.

It has been suggested that in performing gastric resection the site of division should be carried proximal to the incisura angularis (*I.A.* in Fig. 1) to insure low postoperative acidity. If such a resection decreases acidity while at the same time a large portion of the greater

curvature is left in situ, then this procedure would best serve not only to secure reduction of acidity but also to retain resection as a practical technical procedure. In addition, this type of resection would be possible for a large number of surgeons to perform and also, if marginal ulcer should develop, would allow secondary resection to be carried out without too great a hazard. The increasing number of reports showing that marginal ulcer occurs in from 5 to 10 per cent of all cases following gastric resection emphasizes the wisdom of not removing too much stomach at the time of the primary resection. One way to accomplish this is to retain a large portion of the greater curvature. Our studies not only confirm the thesis that removal of the lesser curvature does considerably lower the acidity but also show that retaining a fair portion of the greater curvature does not appreciably alter the result (Table II).

TABLE II

RESECTION ½ TO ⅔ OF STOMACH INCLUDING INCISURA ANGULARIS

	NUMBER	ANACIDITY	LOW ACIDITY	NORMAL OR ADEQUATE ACIDITY*
Gastric ulcer	12	9	3	0
Duodenal ulcer	34	16	9	9
	46	25 (54%)	12 (26%)	9 (20%)
			80%	

*Free hydrochloric acid of 60 degrees or more was considered normal or adequate acid.

Other papers[6, 10-15] may be consulted for a review of the present concepts concerning the physiology of the stomach, but suffice it to say here that up to the present time there has been no adequate explanation for the anacidity that frequently follows subtotal gastric resection. Furthermore, a tremendous amount of experimental work has been done without solving the problem. It is even more difficult to explain why gastric resections that include the lesser curvature above the incisura angularis but that leave one-half to two-thirds of the greater curvature should result in anacidity in almost as high a percentage of cases as do resections of considerably larger portions of stomach.

Studies on the last group of cases (Fig. 1, *C*) i.e., those in which more than two-thirds of the stomach was removed, reveal that approximately 90 per cent of the cases show low or absent acidity, only 10 per cent better than the preceding group (Table III).

TABLE III

RESECTION OF MORE THAN ⅔ OF STOMACH

	NUMBER	ANACIDITY	LOW ACIDITY	NORMAL OR ADEQUATE ACIDITY*
Gastric ulcer	7	7	0	0
Duodenal ulcer	4	1	2	1
	11	8 (73%)	2 (18%)	1 (9%)
			91%	

*Free hydrochloric acid of 60 degrees or more was considered normal or adequate acid.

Our findings show that, although the acidity is affected by the type of resection performed, the results are not so affected and bear little relationship to the postoperative acidity (Tables IV, V, VI, and VII). However, as the postoperative period of time increases, the chances are that more marginal ulcers will develop in those patients who had duodenal ulcer. Furthermore, it is likely that these will occur most often in those patients who have adequate postoperative acidity since, up to the present time, all marginal ulcers observed in this clinic occurred in patients with adequate acidity.

TABLE IV

RESULTS OF RESECTION IN RELATION TO ACIDITY

	NUMBER	PER CENT	SATISFACTORY NUMBER	SATISFACTORY PER CENT	UNSATISFACTORY NUMBER	UNSATISFACTORY PER CENT
Gastric Ulcer (25)						
Low or anacidity	23	92.	22	96.	1	4.
Adequate (normal)	2	8.	2	100.	0	0.
Duodenal Ulcer (63)						
Low or anacidity	32	50.	30	94.	2	6.
Adequate (normal)	31	50.	26	84.	5*	16.
All Cases (88)						
Low or anacidity	55	63.	52	95.	3	5.
Adequate (normal)	33	37.	28	85.	5*	15.

*One died.

TABLE V

CLINICAL RESULTS IN RELATION TO TYPE OF RESECTION

	NUMBER	SATISFACTORY	UNSATISFACTORY
Antral Resection			
Gastric ulcer	6	6	0
Duodenal ulcer	25	21	4 (one died)
Resection of ½ to ⅔ of Stomach Including Incisura Angularis			
Gastric ulcer	12	11	1
Duodenal ulcer	34	29	5
Resection of More Than ⅔ of Stomach			
Gastric ulcer	7	7	0
Duodenal ulcer	4	4	0

TABLE VI

CLINICAL RESULTS IN RELATION TO ACIDITY AND TYPE OF RESECTION

	PER CENT WITH LOW OR ANACIDITY	PER CENT WITH SATISFACTORY RESULTS
Antral Resection		
Gastric ulcer	66.	100.
Duodenal ulcer	16.	84.
Resection of ½ to ⅔ of Stomach Including Incisura Angularis		
Gastric ulcer	100.	91.
Duodenal ulcer	74.	85.
Resection of More Than ⅔ of Stomach		
Gastric ulcer	100.	100.
Duodenal ulcer	75.	100.

TABLE VII

PRE- AND POSTOPERATIVE ACIDITY AND CLINICAL RESULTS IN CASES OF GASTRIC AND DUODENAL ULCER FOLLOWING THE THREE TYPES OF RESECTION DESCRIBED

NUMBER	AGE	PREOPERATIVE ANALYSIS*			POSTOPERATIVE ANALYSIS			AMOUNT RESECTED†	RESULT
		V	F	T					
GASTRIC ULCER									
Patients With Postoperative Anacidity									
1.	47	55	60	75	Anacidity			2	E
2.	32	80	68	76	Anacidity			3	E
3.	38	7	75	100	Anacidity			2	E
4.	58	25	68	83	Anacidity			3	G
5.		42	90	100	Anacidity			2	E
6.	62	60	70	80	Anacidity			2	E
7.	65	?	102	124	Anacidity			2	G
8.	61	60	85	96	Anacidity			3	E
9.	52	52	57	81	Anacidity			2	E
10.	43				Anacidity			2	E
11.	54				Anacidity			1	E
12.	48				Anacidity			3	E
13.	59				Anacidity			3	E
14.	49				Anacidity			3	E
15.	45				Anacidity			2	E
16.	46				Anacidity			1	E
17.	42				Anacidity			3	G
18.	55				Anacidity			2	G
Patients With Low Postoperative Acidity									
					V	F	T		
1.	51	64	64	76	30	50	75	2	E
2.	59	110	83	92	20	45	50	1	E
3.	46	55	94	105	5	14	50	2	F
4.	53	150	59	62	12	40	48	2	E
5.	42				7	44	64	1	E
Patients With Adequate (Normal) Postoperative Acidity									
1.	50	50	96	106	25	111	121	1	G
2.	37	45	90	115	15	98	106	1	G
DUODENAL ULCER									
Patients With Postoperative Anacidity									
1.	47	120	112	130	Anacidity			2	E
2.	52	30	91	107	Anacidity			2	E
3.	52	50	100	107	Anacidity			2	E
4.	54	?	104	145	Anacidity			2	E
5.	45	60	95	110	Anacidity			2	E
6.	48	45	61	79	Anacidity			2	E
7.	52	7	95	105	Anacidity			2	E
8.	57	45	104	120	Anacidity			2	E
9.	50	30	58	70	Anacidity			2	E
10.	40	7	90	100	Anacidity			2	E
11.	24	50	70	85	Anacidity			2	E
12.	52	?	70	85	Anacidity			2	P
13.	52	30	80	138	Anacidity			2	F
14.	44	46	64	74	Anacidity			2	E
15.	54				Anacidity			3	E
16.	35				Anacidity			2	E
17.	28				Anacidity			2	F

*V, Volume
F, Free acid
T, Total acid

†1, Antrectomy
2, Removal of ½ to ⅔, including incisura angularis
3, Removal of more than ⅔ of stomach

TABLE VII—CONT'D

NUMBER	AGE	PREOPERATIVE ANALYSIS*			POSTOPERATIVE ANALYSIS			AMOUNT RESECTED†	RESULT
		V	F	T	V	F	T		
Patients With Postoperative Low Acidity									
1.	41	?	90	92	10	30	33	3	G
2.		50	75	90	12	44	54	2	E
3.	43	21	69	84	10	53	55	2	G
4.	42	21	85	108				1	G
5.	56	100	96	104	6	38	64	2	E
6.	25	50	104	109	8	54	77	3	G
7.	32	?	74	86	15	40	50	2	E
8.	45	20	84	95	5	32	42	2	G
9.	40	30	95	105	20	40	52	2	G
10.	52	81	108	116	15	15	22	2	E
11.	53				15	40	50	1	E
12.	46				7	42	50	1	G
13.	35				37	17	32	2	E
14.	41				10	45	65	2	G
15.	48				25	15	25	2	E
Patients With Adequate (Normal) Postoperative Acidity									
1.	42	250	69	85	40	95	104	1	E
2.	30	56	69	83	60	79	90	2	P
3.	32	45	94	104	30	63	75	1	G
4.	41	75	114	122	35	78	85	1	G
5.	51	30	98	106	30	104	110	1	E
6.	29	?	59	68	50	95	110	1	G
7.	40	35	70	91	20	64	82	1	G
8.	39	92	102	118	115	100	108	3	G
9.	23	20	86	94	17	98	120	2	G
10.	51	7	72	88	40	130	135	2	E
11.	52	?	110	119	25	93	112	2	E
12.	23	23	84	85	40	90	96	1	G
13.	41	7	93	103	30	95	109	1	E
14.	46	90	94	110	40	87	97	1	E
15.	56	29	99	104	18	100	108	1	E
16.	36	55	85	96	20	88	92	1	E
17.	45	105	134	144	95	90	120	2	E
18.	31	45	95	108	35	88	91	1	F
19.	36	65	127	134	65	127	124	2	E
20.	46	30	90	104	22	74	91	2	G
21.	48	?	81	88	35	105	112	1	G
22.	51	?	119	125	20	93	97	1	E
23.	72				70	89	105	1	Died
24.	42				17	80	85	1	P
25.	51				40	70	78	2	F
26.	54				35	93	96	2	E
27.	50				35	90	108	1	E
28.	57				30	70	75	1	E
29.	32				30	90	110	1	G
30.	37				15	95	100	1	G
31.	52				40	60	72	1	G

CONCLUSIONS

In reviewing the results of these three types of resection, we find that removal of the antrum results in reduced acidity or anacidity in only 25 per cent of the patients. Removal of one-half to two-thirds of the stomach plus a portion of the lesser curvature proximal to the re-entrant angle results in 80 per cent of the patients having reduced acidity or

anacidity. Removal of more than two-thirds of the stomach results in 90 per cent of the patients having reduced acidity or anacidity. As previously stated, many advantages in technique are sacrificed when large portions of the stomach are removed, and it seems from our results that little is gained. To retain resection as a useful procedure, we advise that gastric resection be done in such a manner as to insure the highest percentage of cases of postoperative anacidity without sacrificing too much of the stomach. This can be done by removing one-half to two-thirds of the stomach, including a portion of the lesser curvature proximal to the re-entrant angle, and retaining a fair portion of the greater curvature.

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ACUTE ABDOMINAL SYMPTOMS IN ARACHNIDISM

Black Widow Spider Bite

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THE syndrome produced by the bite of the black widow spider (Lactrodectus mactans), when duly recognized, is not a surgical problem. However, because of the abdominal symptoms usually resulting from arachnidism and the fact that the patient often attaches little or no significance to the spider bite, it behooves all surgeons to be familiar with the clinical picture of this condition if needless operations are to be avoided. Morton,[17] in a careful study of the cases observed at the University of Virginia Hospital, stated that "The most outstanding symptom in each case was the severe and usually cramplike abdominal pain; while the most important physical abnormality was the extreme boardlike rigidity of the abdominal musculature." Noland[19] emphasizes that patients with arachnidism are often sent to a hospital by the referring doctor with a diagnosis of some acute surgical condition of the abdomen. Patients suffering from arachnidism are occasionally subjected to celiotomy. It appears from the recent reports of D'Amour and his associates,[10, 11] Kirby-Smith,[16] and Frank[21] that the incidence of arachnidism is increasing. In spite of these facts the subject has received very little attention in the surgical literature.

THE SPIDER

Lactrodectus mactans is a common spider which may be found throughout the United States and in Canada.[15, 16] This spider may be found in woods and fields but is also not infrequently seen about protected areas such as garages, basements, and outhouses. The reason more individuals are not bitten is due more to the characteristics of the spider than to any lack of its presence in various localities. The black widow spider is a timid creature and seldom bites a human being except when crushed or contacted in the dark. If the web of this spider is disturbed, usually the creature retreats and shows little inclination to bite. In turning over old planks, logs, or rocks, individuals may make sudden contact with the spider and be bitten. Many people have been bitten in outdoor privies where in the dark the individual came in contact with the spider.

The Lactrodectus mactans female which is the poisonous member of the species may be identified by its black color and bright red hourglass marking on the ventral surface. The abdomen of the female is

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larger than the male. D'Amour and co-workers[10] and Blair[6] give good descriptions of the life cycle and characteristics of the black widow spider. It has been reported by D'Amour and co-workers[10] that the dried black widow venom is, weight for weight, fifteen times as poisonous as is rattlesnake venom. The dried residue from the venom of one spider weighs .064 mg. The toxic principle of the venom is a protein, probably an albumin. Hall[13] states that the toxin is a nonhemolytic neurotoxin which apparently exerts its effects on nerves and nerve endings.

SYMPTOMS OF ARACHNIDISM

The pain produced by the bite is often described as resembling the pain from a pinprick or a small splinter. Frequently patients may pay little or no attention to the bite and may not give the incident in reciting the history of their illness unless specifically questioned. The local lesion may appear as a small red pin-point area or may be invisible. Usually in from one-half to two hours the individual complains of cramping pains which have their origin in the muscle groups near the location of the bite. When bitten on a lower extremity or the genitalia the cramps are first noted in the thighs and hips. In a short time the pain is apt to spread to the abdomen and to be excruciating in intensity. Patients with this condition often appear to have pain comparable in severity to that caused by renal colic, perforated ulcer, or coronary occlusion. A careful history may be difficult to obtain because of the severity of the pain. Further questioning usually reveals severe pain in the thighs, back, and lower chest as well as in the abdomen. The abdominal examination shows the presence of boardlike rigidity although the abdomen usually moves with respiration.[2, 5] Also, there is less tenderness than one would expect to be present in peritonitis producing such marked rigidity. The temperature is apt to be normal when the patient is first seen but fever is likely to develop a few hours later, usually being about 100° F., although occasionally patients have temperature of 101 or 102° F. There may be nausea and vomiting but these symptoms occur less frequently than might be expected in patients exhibiting such marked abdominal rigidity. Leucocytosis of a moderate degree is usually present.

TREATMENT

The great majority of patients recover completely from arachnidism in from one to three days with conservative measures regardless of the particular form of therapy used. The large variety of remedies which have been recommended speaks for the inefficiency of most of the agents in producing relief. Morphine sulfate in doses of ¼ and ½ gr. for an adult frequently gives only partial relief of pain. Magnesium sulfate has often been used intramuscularly in patients with arachnidism with but little evidence of improvement. Intravenous calcium gluconate is recommended by many but exerts relatively little effect on the patient's

general condition. Spinal puncture also has been used without evidence of definite improvement. Frequent hot baths have been found to be a real help in making these patients comfortable.

Specific Lactrodectus mactans antiserum when used relatively soon after the bite has been received, now seems to offer the best opportunity for reducing the morbidity of the condition and of making the patient comfortable. Noon and Minear[18] reported spectacular improvement in six patients receiving specific antiserum when given relatively soon after the bite. Kirby-Smith[22] has also observed marked improvement following the use of specific antiserum in several patients in which it has been used since his report published in February, 1942. Specific antiserum gave relief of pain and subsidence of abdominal rigidity in four children reported in Table I. No beneficial results were observed in one adult that received antiserum. The animal experiments of Hall[13] using specific antiserum, support the clinical observations that to be efficacious the antiserum must be used early. Bogen[8] reported "encouraging results" from the use of human immune serum. However, D'Amour[11] showed experimentally that human immune serum is far less potent than the specifically prepared antiserum.

END RESULTS

As stated above, the great majority of patients with arachnidism recover without sequelae in from one to three days. The mortality rate of 6.6 per cent as given by Bogen and frequently quoted in the literature appears to be erroneous. These deaths were not collected from established reports in the literature but were collected from newspaper articles, death certificates, and personal communications.[9] Kirby-Smith reports no deaths among 284 cases collected from the literature by various authors.[16]

Fatalities do occur, although they must be relatively unusual. Noon and Minear[18] and Kirby-Smith[16] each report one fatal case. Beasley[4] recently reported a death ascribed to arachnidism and gave the autopsy findings in the case.

COMMENT ON TABLE I

The fifty-six cases reported in Table I were seen in the John Gaston Hospital, Memphis, Tenn., between 1933 and 1942 inclusive. The clinical picture presented by this group of patients was essentially that which has been outlined above. Twenty-five of the patients were bitten on either the buttocks or the genitals. Severe abdominal pain was the most important symptom and boardlike rigidity was usually found to be present on abdominal examination. Occasionally patients showed normal temperature charts. The patients in thirty-one of the fifty-six cases studied had a maximum temperature of 99 to 100° F., while nine developed fever of 101° F. or above. Five patients had nausea and vomiting. Leucocytosis was usually present. No significant changes were found on examination of blood pressure, spinal fluid, or urine.

TABLE 1

BLACK WIDOW SPIDER BITE

NO.	AGE	SEX	MONTH	BODY LOCATION	TIME SYMPTOMS DEVELOPED	MAXIMUM TEMPERATURE (DEGREES F.)	W.B.C.	SYMPTOMS
1	30	M	Oct.	Penis	½ hr.	99.8	7,500	evere pain in thigh and chest; mild abdominal pain
2	24	M	Nov.	Ring finger	15 min.	99.0	6,600	Nausea, vomiting, pain in arm, back, and abdomen; abdominal rigidity +++
3	27	M	July		½ hr.	99.0	7,200	Inguinal, abdominal cramps; abdominal rigidity ++++
4	45	M	Aug.	Penis	10 min.	100.0	7,150	Pain in abdomen, generalized aching; slight abdominal rigidity
5	34	M	Sept.	Penis	20 min.	99.0	9,900	Inguinal, abdominal cramps, backache, and abdominal rigidity
6	16	M	Sept.	Penis	Not known	101.0	11,760	Nausea, backache, and slight abdominal rigidity
7	40	M	Sept.	Penis	15 min.	99.4	18,500	Vomited 3 times, pain in thighs and abdomen; abdominal rigidity ++++
8	15	M	Sept.	Penis	45 min.	99.8	21,400	Vomited 3 times, pain in knees and back; abdomen rigid ++++
9	52	M	Nov.	Penis	20 min.	99.6	7,400	Nausea, abdominal pain; slight abdominal rigidity
10	50	M	Nov.	Neck	30 min.	99.0	4,100	Pain in back, legs, abdomen; abdominal rigidity ++++
11	21	F	Nov.	Breast	30 min.	99.4	15,120	Vomited 2 times, cramping pains in abdomen and chest; pain in thighs and legs
12	22	M	May	Penis	½ hr.	100.0	12,250	Acute pain in abdomen, pain in thighs and back; abdominal rigidity ++++
13	19	M	June	Buttock	3 min.	101.0		Abdominal pain, no rigidity; increased tone
14	37	M	Aug.	Penis	30 min.	99.4	9,850	Cramps in legs, thighs, abdomen; abdominal rigidity +++
15	22	M	Sept.	Foot		98.8		

TABLE I—CONT'D

NO.	AGE	SEX	MONTH	BODY LOCATION	TIME SYMPTOMS DEVELOPED	MAXIMUM TEMPERATURE (DEGREES F.)	W.B.C.	SYMPTOMS
16	35	M		Buttock				Abdominal pain, rigidity
17	37	F	May	Buttock	½ hr.		8,850	Abdominal cramps
18	22	M	May	Arm	½ hr.	103.0	14,250	Abdominal pain and rigidity
19	29	M	Oct.	Wrist	1 hr.			Pain in arm and abdomen; abdominal rigidity ++
20	29	M	July	Penis	½ hr.	100.0	11,300	Pain in abdomen and chest, and headache; abdominal rigidity ++
21*	37	M	Aug.	Knee		98.8	8,300	Abdominal rigidity ++++
22	40	M	Sept.			98.8		
23	50	M	June			100.0		Abdominal pain and rigidity
24†	20	M	Aug.	Penis	½ hr.	97.0	20,000	Vomited once, pain in hips, abdomen, back; abdominal rigidity ++++; *no distension*
25	40	M	Oct.	Foot	5 hr.	100.0	5,300	Pain in hips and back, abdomen flat; abdominal rigidity ++++
26	27	M	Oct.	Penis	½ hr.	102.4	8,200	Pain in legs, hips, abdomen; abdominal rigidity ++++
27	45	M	Oct.		½ hr.			Generalized aching; abdominal colic 4 hours after bite
28	44	F	Oct.	Leg	1 hr.	101.8	7,900	Nausea, no vomiting, severe abdominal pain, abdomen distended, tender, some rigidity; aching in legs, back, and chest
29	22	M	Oct.	Scrotum	10 min.	100.0	12,700	Pain in inguinal region, through chest and abdomen; abdominal rigidity +++
30	40	M	May	Penis	½ hr.	99.0	8,200	Cramps in abdomen and back; abdominal rigidity ++++
31	49	M	July	Axilla		99.4		Neck pain
32	20	M	Nov.	Toe	10 min.	98.8	15,050	Severe pain in groin; abdominal rigidity ++
33	16	M	June	Back		100.0	11,550	Abdominal cramps and rigidity ++
34	34					100.0	12,800	Pain in back and abdomen; abdominal rigidity ++

35	12	M	April		10 min.	100.4	10,600	Pain in back and abdomen
36	50	M	May			98.8		Cramps in leg and abdomen
37	22	M	April	Scrotum			8,750	
38	32	M	July				11,400	Abdominal pain and rigidity; tenderness
39	38	M	Aug.	Penis	10 min.	99.4	7,800	Generalized aching; abdominal cramps and rigidity ++
40	19	M	Oct.	Toe	10 min.	99.0	10,200	Pain in hips, abdomen, and epigastrium; not tender but rigid +++
41	19	M	April	Penis	10 min.	100.2		Abdominal rigidity +++
42	18	F	June			99.6	7,350	Pain in back and abdomen, no tenderness; abdominal rigidity
43	26	M	April		45 min.	99.4		
44	12	M	Oct.	Hip	30 min.	100.0	9,500	Severe abdominal pain, no vomiting; abdominal rigidity ++++
45	12	M	Oct.	Arm	30 min.	101.0	6,900	Severe cramps in hip and abdomen; abdominal rigidity +++++
46	10	F	Nov.	Thigh	1½ hr.	100.0	21,000	Severe pain in hips and abdomen; abdominal rigidity +++++
47	46	M	Dec.	Ankle	3½ hr.	100.2		Aching cramps in thigh, back, and abdomen; rigidity ++
48	28	M	Nov.	Penis	2 hr.	101.0	7,400	Pain in hips and abdomen; abdominal rigidity +++
49	31	F	Nov.	Nose		99.4		Chest pain
50	48	M	Nov.	Nose	½ hr.	99.0		Pain in neck, abdomen, and chest
51	64	M	Oct.		1 hr.	99.2		Muscle cramps in extremities; abdominal cramps
52	15	F	Oct.	Forehead		98.8		Pain in head and neck
53	2	M	June	Penis		101.0		Infection of penis for four days; seen 4 days after bite
54	67	M	July	Penis	1 hr.	99.0	11,700	Severe upper abdominal pain with rigidity ++++; vomiting
55	58	M	June	Scrotum	2 hr. mild 10 hr. severe	101.0	5,850	
56	28	M	Nov.	Arm		98.8		Back and abdominal pain; abdominal rigidity

*Exploratory laparotomy—preoperative diagnosis, perforated ulcer.
†Exploratory laparotomy—preoperative diagnosis, perforated appendix.

The therapeutic agents used varied considerably in the series. Morphine, atropine, magnesium sulfate, calcium gluconate, specific antiserum, and repeated hot baths were among the methods used. Morphine, hot baths, and specific antiserum when given relatively early seemed more advantageous in treatment than the other methods. Two patients were subjected to celiotomy, the preoperative diagnosis being perforated ulcer in one and perforated appendix in the other. There were no fatalities in this series.

SUMMARY AND CONCLUSIONS

The severity and predominance of abdominal symptoms and signs in patients with arachnidism make it necessary that surgeons have a clear conception of the condition if needless operations are to be avoided. Patients, although aware of spider bite, often fail to realize the causal relationship between bite and symptoms. The absence of abdominal tenderness and the presence of movement of the abdomen with respiration are important differential features in recognizing the syndrome. Specific antiserum given early after the bite seems to be the most rational therapy at this time. Fifty-six cases without a fatality are reported.

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AN EVALUATION OF SOME OF THE MATERIALS COMMONLY USED FOR THE PREOPERATIVE PREPARATION OF THE SKIN*

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THAT methods for evaluation of skin antiseptics have been generally unsatisfactory is evidenced by the voluminous literature on the subject and by the great variety of antiseptics which are employed for skin preparation in hospitals throughout the country. The main reason for this unsatisfactory state of affairs is that the conventional methods of evaluating skin antiseptics in vitro, while failing to meet the practical test of the action of the antiseptic on the skin, have nevertheless been used to promote the sale of commercial antiseptics.

At the same time, with so many far more dramatic fields of research open to the student of surgical problems, the investigation of skin antiseptics has not been systemically pursued by many individuals with adequate bacteriologic equipment and, at the same time, the point of view of the practicing surgeon. The work of Philip Price, of Baltimore, is the outstanding exception.

In choosing an agent for skin sterilization, the surgeon may relegate to positions of secondary importance the assembled data on the test-tube effectiveness of the various preparations, since the conditions employed resemble only in remote fashion the conditions provided by the skin itself. Furthermore, the surgeon will bear in mind the practical conditions under which antiseptics are employed clinically, particularly for supplementing the cleansing action of the preoperative scrub, and for preparing the skin of the operative field. The surgeon will require that the substance be active against skin flora, whether pathogenic or nonpathogenic, since the distinction is only a relative one; that it have a low surface tension, so as to make intimate contact with the skin; that it be active in the presence of organic material *and soap*; that it do more than produce a sterile film on the skin surface, beneath which bacterial proliferation continues; that it not be irritating to the scrubbed skin; and, finally, that the cost of the quantity necessary for practical conditions should not be excessive.

It might have appeared unlikely that any experimental method could be found which would simultaneously take into consideration all of the

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above factors. However, at about the time we decided that some work must be done on this problem, Price published a new method which seemed to us to provide new and sound principles, and we, therefore, used his technique as a starting point in our own work.

In the Price method, counts of the number of bacteria washed off during each of a series of one-minute scrubs are obtained by subjecting the wash water from each period to a standard plate count procedure. After determining the standard rate of removal of bacteria from the skin with soap and water alone, one may apply any given antiseptic and see to what extent this antiseptic modifies the subsequent rate of removal of bacteria. The advantage of this method is that it actually tests the antiseptic on the skin; and, by modifying the time of application of the antiseptic and by using many individuals as test subjects, it is possible to take into consideration all of the factors which were indicated above. The chief disadvantages of the technique are that it is very tedious and the production of results is necessarily slow because no one individual can carry out more than one experiment per week. The latter limitation is a result of the necessity for allowing time for regeneration of skin flora after vigorous scrubbing and "degermation."

METHOD

In order to simplify the description of the experimental technique which was finally adopted we will list the essential materials and supplies:

15 sterile basins
15 sterile brushes
15 lots of Ivory Snow, 1 Gm. each
Tubes of broth culture media, 4 c.c. each*
Tubes of melted nutrient agar, 9 c.c. each†
Sterile enamel cups for antiseptics under test
Sterile gauze sponges and sterile towels

Procedure.—The "scrubber" stands on one side of a laboratory table placed adjacent to the sink, and facing the assistant. Necessary materials are arranged within reach. After preliminary moistening of the forearms and hands, 1 Gm. of Ivory Snow is placed on a moistened sterile brush and a cycle of scrubbing is commenced which is accurately timed with a stop watch. After a few seconds devoted to working up

*Neopeptone broth:

Distilled water	1 L.
Neopeptone	25 Gm.
Dextrose	0.5 Gm.

Adjust pH to 7.3

†Nutrient agar:

Distilled water	1 L.
Neopeptone	1 Gm.
Sodium chloride	8.5 Gm.
Glycerin	10 c.c.
Agar	15 Gm.

Adjust pH to 7.4 or 7.8
Add 0.5 c.c. horse serum to melted agar immediately before pouring plate

a lather in the moistened palm, the palm and fingers are scrubbed for five seconds; the nails for five seconds; the back of the hand for five seconds, and the forearm for fifteen seconds. The brush is then placed in the scrubbed hand and a similar procedure is carried out on the other hand and arm. The assistant then rinses the lather from the hands and forearms with a liter of tap water, the rinse water being collected in a sterile basin. The assistant withdraws two 1 c.c. samples of wash water and places them in each of two tubes of broth in order to remove the bacteria, as rapidly as possible, from the concentrated solution of soap. While the assistant is carrying out this procedure, the scrubber selects another brush and prepares to carry out another cycle of scrubbing. These cycles may be repeated for as many intervals as desired. In obtaining control data on soap and water alone, it is necessary to have about fifteen of these cycles. In experiments involving evaluation of an antiseptic, the scrubbing cycles are interrupted at some arbitrary interval, such as at the end of ten minutes or cycles. At this time, the hands and forearms are thoroughly dried with a sterile towel. The antiseptic is applied with a saturated sponge, the period of application being timed with a stop watch. In our experiments, we have also timed the period of drying of the antiseptic. Any unfixed antiseptic is then washed off with a liter of tap water and the series of scrubbing cycles is resumed, usually for five additional minutes. After completion of the entire period of scrubbing, the tubes of broth are thoroughly shaken exactly forty times with violent agitation and 1 c.c. of the mixture of soapy water and broth is placed in a tube of melted agar. The agar is poured out into a Petri dish which is subjected to standard manipulation in order to obtain uniform distribution of its contents. The agar plates are allowed to harden and are then incubated in an inverted position for forty-eight hours at 37.5° C. After the plates are counted, it is possible, after averaging the values of each pair of plates, to calculate the number of bacteria per cubic centimeter of wash water at each specific phase of the scrubbing period.

This procedure differs from Price's method in employing measured quantities of water and soap and in the use of individual sterile brushes for each scrubbing cycle. We have also provided for rapid separation of the test sample from the soapy water in order to avoid the deleterious effect of the alkaline soapy solution on the bacteria. These modifications do not alter the basic principle of the procedure, but are designed to improve the accuracy of the results.

Method of Calculation.—In Price's reports, the results of each scrub are subjected to a rather complicated mathematical procedure through which he arrives at an estimate of the total number of bacteria remaining on the skin of the hands and forearms at each given cycle in the scrubbing period. Even with the revision in methods of procedure which we have employed, we have not been able to satisfy ourselves that the experimental technique is of sufficient mathematical accuracy

to justify this type of computation. There is so much variation between individuals and between different scrubs by the same individual, that any final conclusion must be based on averages of many experiments if it is to enjoy real significance. After trying out a number of different methods of calculation, we finally concluded that the one most satisfactory, within the limits of accuracy of the procedure, is as follows.

1. We have ignored the wash water counts obtained during the first five minutes of scrubbing. This is the time during which the greatest variation takes place, and the magnitude of the counts is dependent upon many variable factors, most important of these being the length of the time interval since the preceding scrub.

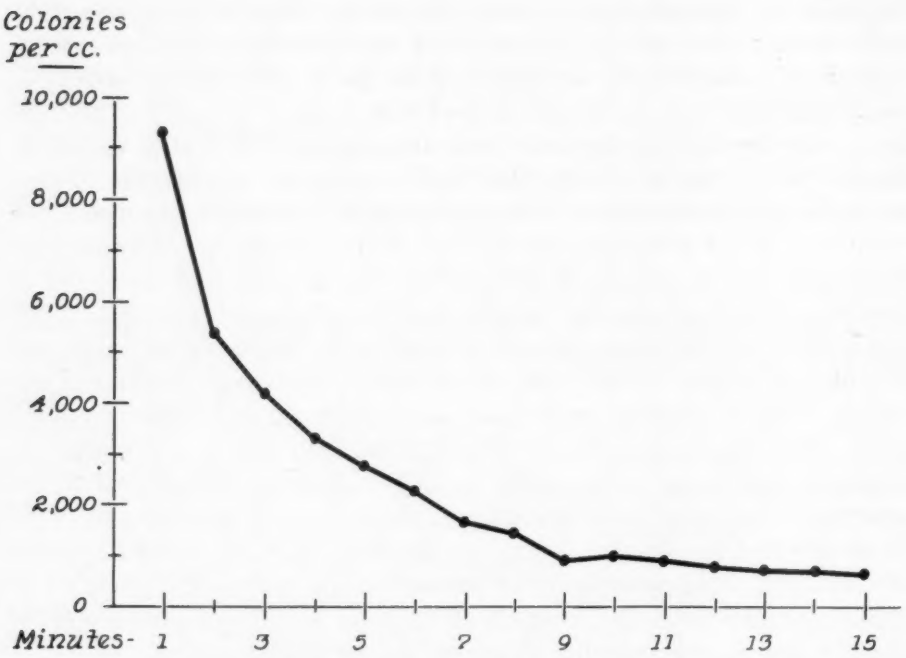

Fig. 1.—Determination of R_1 for average of thirty-six scrubbing experiments of fifteen minutes each.

2. We have found in 226 experiments that the number of bacteria removed during the second five minutes of scrubbing is reasonably constant for different individuals and in different scrubs by the same individual. The average rate of removal of organisms is about 1200 per c.c. per minute or cycle during the eighth minute or cycle, and about 900 per c.c. during the tenth minute. At this point the disappearance curve tends to approach the horizontal (Fig. 1). Even though scrubbing with soap and water alone is continued for as long as thirty minutes, one would continue to remove bacteria at the rate of about 200 per c.c. per minute. We have designated the curve represented by the second five minutes of scrubbing as R_1, a curve which drops from the value of roughly 1800 per c.c. per minute during the sixth minute to about 900

per c.c. per minute during the tenth minute. An additional five minutes' scrubbing would reduce this to about 600 per c.c. per minute. R_2 designates the final five minutes or cycles of scrubbing *after the application of the antiseptic.* Since the curve is almost horizontal at this point, particularly after the application of an effective antiseptic, one may average together the bacterial counts for the last five minutes into a single figure for each of the experiments. When values for R_2 from a number of different experiments with the same antiseptic are averaged together, one arrives at a figure which characterizes the effectiveness of the antiseptic agent. The acceptability of this method of calculation is due to the fact that the best skin antiseptics afford R_2 values of less than 10 bacteria per cubic centimeter per minute in contrast to the control values which are never less than 500 to 600 bacteria per cubic centimeter per minute. The lower the value of R_2, the greater the effect of the antiseptic. The validity of this conclusion depends in part upon the reasonable but unproved assumption that the rate of removal of pathogenic bacteria from the skin at any given time is dependent upon the number of living bacteria on the skin at that time.[5]

RESULTS

In order to simplify the presentation of a somewhat unwieldy mass of data, we present Tables I, II, and III. These state the number of

TABLE I

DETERMINATIONS OF R_2 FOR SOME COMMERCIALLY AVAILABLE ANTISEPTICS*

SUBSTANCE	NO. OF EXPERIMENTS	AVERAGE R_2	RANGE OF R_2
Tincture "Q" p-chloro-symm.m-dimethyl hydroxybenzene p-tert. amyl hydroxybenzene and neutral soap. Solution 5% in 70% alcohol by weight	3†	168	90-240‡
Tincture "Q" 1% aqueous solution	4	377	197-636
Tincture "Q" 5%	6	270	145-423‡
Tincture "X" Mixture of high molecular alkyldimethylbenzyl ammonium chlorides	3†	220	123-265
Tincture "S" 2-Furylmercuric hydroxide	6	123	68-200
Tincture "V" 1% 4-Nitro-anhydro-hydroxymercuri-ortho-cresol	4	137	37-270
Tincture "T" Secondary amyl tricresols .1% ortho-hydroxyphenyl mercuric chloride .1%	3†	79	30-106
70% Ethyl alcohol by weight	9	194	85-415
95% Ethyl alcohol	4	86	17-169

*1 minute exposures (30 second application; 30 second drying).
†Series not complete.
‡Marked irritation.

experiments of each type, the average value for R_2 for these experiments, and the range of variation of the R_2 figures. Table I concerns experiments in which the antiseptic was applied for thirty seconds and allowed to dry for thirty seconds. Table II is concerned with a larger number of experiments in which the antiseptics were applied for two minutes and allowed to dry for two minutes. It is noted that in some cases the range of variation is great, whereas, in others, all of the values obtained in seven to nine experiments are consistently low.

TABLE II

DETERMINATIONS OF R_2 FOR SOME COMMERCIALLY AVAILABLE ANTISEPTICS*

SUBSTANCE	NO. OF EXPERIMENTS	AVERAGE R_2	RANGE R_2
Tincture "X"	6	111	17-242
Tincture "U" Sodium ethyl-mercuri-thiosalicylate	9	123	20-463
Tincture "V"	9	32	5- 55
Tincture "W"	7	35	24- 68‡
Tincture "T"	9	27	6- 66
Tincture "S"	9	24	7- 47
Chrysoidin Y mixture	9	46	19- 80‡
70% Isopropyl alcohol	9	20	21- 31
70% Ethyl alcohol (by weight)	10	18	3- 56
95% Ethyl alcohol	10	12	6- 27
Tincture iodine followed by 95% ethyl alcohol†	7	7	5- 9

*4 minute exposures (2 minute applications; 2 minute drying).
†Iodine applied for 30 seconds.
‡Marked irritation.

Time of Application.—A glance at Tables I and II shows that the R_2 values are much lower with four minutes' exposure than with one minute exposure. Furthermore, it seems to be generally true that the agents which are most effective with the brief period of exposure are also most effective with the longer period of exposure. Besides emphasizing the obvious importance of the time of action in chemical antiseptics, this relationship of the figures tends to uphold the general validity of the technique.

Mercurial Agents.—Five proprietary tinctures of mercurial antiseptics were included among the agents studied. It was pointed out by Price[4] that some mercurial agents, particularly bichloride of mercury, are capable of producing a sterile surface on the skin as a result of the formation of a surface coagulum which may remain intact for a considerable period of time. However, it was believed that bacterial proliferation could take place at an active rate beneath this film, and that the end result would likely be a higher population of bacteria in the skin than would have been the case had the mercurial agent not been applied. One advantage of the experimental technique employed by Price and by us is that vigorous mechanical scrubbing will remove this surface film and release bacteria which might otherwise remain behind the superficial barrier. No data were obtained concerning the duration

of the action of the several agents, our emphasis being placed primarily on the immediate effect.

The mercurial antiseptics employed as the commercial tinctures were, as a group, in the intermediate range of effectiveness, as shown in Table II. Of these agents, tincture S showed a slight, though possibly significant, advantage over the other agents in this group, namely tinctures T, U, V, and W. Tincture U appeared quite consistently to be the least effective of the mercurial preparations. Where the period of exposure to the antiseptic was only one minute, the differences between the several mercury-containing preparations are not significant, although tincture T appeared to be most active. The vehicle of tincture S was tested and was found to have an average R_2 in four experiments of 113 with a range of 74 to 138, indicating that it was markedly less effective than the complete preparation.

*Chrysoidin Y Mixture.**—Slightly less effective than the mercurial agents was chrysoidin Y mixture, which happens to be an antiseptic now in common use in several Philadelphia hospitals. The average R_2 figure of forty-six is higher than four out of five of the mercurial agents. Though one of the prevailing arguments for its clinical use, in addition to its recognized inexpensiveness, has been its freedom from irritation, it was noted that the application of this substance to the skin for four minutes resulted in irritation, particularly of the skin of those individuals with light complexions.

Tincture X.—The agent, tincture X, has been the subject of a number of highly enthusiastic reports[3, 6] and there is no question but that under certain experimental conditions it possesses very powerful antiseptic qualities. However, in our hands, it has been a decidedly limited value when applied to the freshly scrubbed skin. This is possibly due to the fact that it is known to be inactivated by soap.[3] We made no attempt to exclude soap from the skin before applying any of the antiseptics because of the fact that soap is still the detergent most commonly used in preoperative skin preparation. It would seem most undesirable to rely for skin sterilization on an agent which was incompatible with traces of soap. This does not imply that tincture X may not be of definite value in other types of sterilization.

Alcohols.—As a group, the most effective preparations were the alcohols. This fact coincides with the findings of Price.[2] He recommended the use of ethyl alcohol of 70 per cent by weight, and believed that the effectiveness of the alcohol might possibly be increased by adding a certain amount of isopropyl alcohol.[2] In our experiments, the effectiveness of 70 per cent alcohol by weight was exceeded only by that of 95 per per cent ethyl alcohol. In this respect, our findings differ from those of

*Chrysoidin Y — 2 Gm.
Bichloride of mercury — 1 Gm.
Concentrated HCl — 7.5 c.c.
Acetone — 100.0 c.c.
Ethyl alcohol — 525.0 c.c.
Distilled water, q.s. — 1,000 c.c.

Price, and from the prevailing impression that 70 per cent alcohol is a more effective antiseptic than is 95 per cent alcohol. When exposure was limited to one minute, 95 per cent alcohol appeared to be very much more effective than 70 per cent alcohol. The difference was not as significant when the period of exposure was increased to four minutes. It was observed that when the 95 per cent alcohol was allowed to dry, the R_2 tended to be lower than was the case when water was applied before the drying of the alcohol had been completed. When the drying was not completed, there appeared little difference between 70 per cent by weight alcohol and 95 per cent alcohol (Table III). Seventy per cent isopropyl alcohol possessed approximately the same degree of antiseptic effectiveness as 70 per cent by weight ethyl alcohol.

TABLE III

DETERMINATIONS OF R_2 FOR ETHYL ALCOHOL*

SUBSTANCE	NO. OF EXPERIMENTS	AVERAGE R_2	RANGE R_2
95% Ethyl alcohol			
Allowed to dry	10	12	6-27
Drying avoided	4	26	17-48
70% Ethyl alcohol (by weight)			
Allowed to dry	10	18	3-56
Drying avoided	3†	21	18-24

*Two minute exposures.
†Series not complete.

Iodine.—The effectiveness of 95 per cent alcohol was increased slightly but definitely by a preliminary application of tincture of iodine. In seven experiments with iodine followed by 95 per cent alcohol, the average R_2 was seven and the maximum R_2 obtained was nine. Both in respect to the average figure and the maximum figure, this combination of iodine and 95 per cent alcohol was superior to any other preparation studied. Iodine is the antiseptic which has probably enjoyed more general use over a long period of time than any of the other skin antiseptics. It is interesting to note that laboratory studies of the type here reported serve to point out that the trend away from iodine to more expensive and complicated preparations has not been based on sound evidence. While iodine is undesirable for use by the surgeon in preparation of the skin of the hands and forearms because of its staining properties, there is every reason to believe that tincture of iodine is the most desirable agent for preparation of the skin of patients in the operating room. According to our figures, it may be desirable to remove the tincture of iodine with 95 per cent alcohol in order both to reduce the irritating properties of the iodine and also to augment the effectiveness of the skin preparation.

*Tincture Q.**—A modified phenol preparation known to be compatible with soap was included in the series in order to have data on a repre-

*Kindly supplied by Lehn & Fink Products Corp., Bloomfield, N. J., under the trade name, "Amphyl," through the courtesy of Dr. E. G. Klarmann.

sentative of this group. The material studied was a preparation containing p-chloro-symm.m-dimethyl-hydroxy-benzene, p-tert. amyl-hydroxy benzene and neutral soap. Both aqueous solutions and tinctures of this preparation were studied. It proved to be virtually without effect on the skin, and, in fact, the vehicle in which the tincture was dissolved proved to be just as effective as the tincture containing the supposedly active agent. When the strength of the material was increased to a point at which some slight degree of effectiveness appeared, the preparations were found to be quite irritating to the skin and could not be tolerated. When a 5 per cent tincture of the material was incorporated with 70 per cent by weight ethyl alcohol, conceded to be an effective antiseptic, the resulting mixture was found to be almost identical in effectiveness with the 70 per cent alcohol alone.

DISCUSSION

Although it would be desirable to have a method of evaluating skin antiseptics by which comparison might be made on a more accurate mathematical basis than that here described, we are inclined to believe that this comes as close to providing a simple and satisfactory test method as any that has been put forward. In its future application, the method could undoubtedly be simplified. For example, if a preliminary scrub of ten minutes were carefully conducted, the antiseptic then applied, and careful bacterial counts obtained on the wash water for a period of five minutes after the application of the antiseptic, a series of reduplicated tests would provide a satisfactory estimation of the practical efficiency of any agent proposed for skin sterilization. We emphasize the necessity for carrying out bacterial counts for at least five successive minutes of scrubbing in order to eliminate sources of error inherent in any method of collecting and counting bacteria. Furthermore, it is desirable that the tests be carried out by several different individuals and that a total of at least four experiments be carried out with each individual preparation if reliable interpretations are to be obtained. It must be emphasized that satisfactory results will only be obtained if the scrubbing cycles are conducted with careful precision, and if the bacteriologic procedure is carried out in accordance with sound practices.

It is not the purpose of this paper to enter into a discussion of the reasons why the alcohol preparations appear to be more effective than any of the commercial antiseptics tested. While skin preparation is unquestionably the widest field of use for chemical antiseptics of the types here considered, there are undoubtedly certain fields of usefulness for antiseptics in which alcohol is entirely unsuitable. Furthermore, it is possible to use alcohol in strengths of 70 to 95 per cent, while the concentration of active agent in most tinctures is only a fraction of 1 per cent. The surgeon is concerned, however, with the elementary question of what method of preparation will result in the least possible number of living organisms on the skin of the operating personnel and on the

skin at the site of the operation. Furthermore, he must rely on agents which will be well tolerated by the skin and, in testing them, must employ the concentrations sold commercially. With these considerations in mind, we are inclined to recommend that principal reliance be placed on soap and water and ethyl alcohol in the preparation of the skin of operating personnel. Since the skin of the patient is not scrubbed for ten minutes, it is probably advantageous to precede the alcohol treatment with an application of 3.5 per cent tincture of iodine. The ideal concentration of alcohol is 95 per cent, but, for reasons of economy, it may be necessary to reduce the concentration to 70 per cent by weight. Such a compromise can be made without sacrificing more than a fraction of the effectiveness of the material.

We urge, also, that in the use of alcohol and in other skin antiseptics, the surgeon recognize the fundamental importance of the factor of time. Two minutes of continuous application of the alcohol to the skin is desirable, preferably accompanied by mechanical rubbing. The alcohol should be left to evaporate in order further to extend the period of its actions.

CONCLUSION

Through a modification of the Price technique by which the effectiveness of antiseptics on freshly scrubbed skin is evaluated, it is concluded that ethyl alcohol in strengths of 95 per cent and 70 per cent by weight is preferable to any of a group of commercially prepared agents specifically designed for skin sterilization.

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RESECTION OF THE COLON IN SIX CASES OF HIRSCHSPRUNG'S DISEASE

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THE treatment of Hirschsprung's disease has undergone some changes in the last two decades. While it is certain that no one form of treatment is helpful to all cases, there is now, with more variety of treatment, a greater chance of benefiting every patient. However, medical management was very unsatisfactory until the development of the newer autonomic system drugs such as the parasympathetic drug, mecholyl (Law[1]), and sympathetic drug, syntropan (Klingman[2]). Since Law's[1] report, in 1940, not many cases in which this treatment was used have appeared in the literature but it is likely more will. Drug therapy is in large part a trial-and-error type of treatment as there is no way of being certain whether the parasympathetic system is underactive or the sympathetic overactive, although spinal anesthesia may be diagnostic in determining overactivity of the sympathetic system. However, one drug or the other is usually helpful in the mild or early cases and possibly could keep the condition in check if begun early in infancy.

Since 1927, when Wade and Royle[3] reported the first operation for removal of the lumbar sympathetic ganglion in the megacolon, surgical treatment of Hirschsprung's disease has consisted primarily of this operation. The literature since 1930 has contained an increasing number of reported "cures" of megacolon and even chronic constipation following this operation. One wonders how many failures are omitted from the literature. The operation for resection of the affected part of the colon is mentioned only to be condemned except in the report by Dixon[4] and in the book by Ladd and Gross.[5]

The two main reasons for the disrepute of this operation are first, the high operative mortality and second, the likelihood that the condition may recur in the portion of the colon remaining. Perhaps the first situation may have been true fifteen or twenty years ago but should not be now. We are of the opinion that the second can perhaps be prevented by the better medical program now available.

Of pediatric as well as surgical interest is the variability of signs of Hirschsprung's disease in the first few weeks of life. At times the onset

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of constipation and distention may be late and the presenting sign may be vomiting. In our series of six cases the early severe vomiting was a pronounced feature in four (Cases 1, 2, 3, and 4) of the infants. This may be just another manifestation of motor imbalance of the gastrointestinal tract which as it progresses tends to localize in the lower rather than the upper tract.

Since two of our patients did not respond to bilateral lumbar sympathectomy and the other four did not respond satisfactorily to medical treatment, surgical resections were done. In the following case reports all laboratory reports were normal except as indicated. Proctoscopic examination was routine and was always negative for any evidence of obstruction. The sigmoid was uniformly dilated. The pathologic report on the resected portions of colon was similar in all cases, that is, muscular hypertrophy with round cell infiltration and no change in nerve cells. These findings were typical of those of Hirschsprung's disease.

CASE REPORTS

CASE 1.—T. P., a male, first entered this hospital Sept. 22, 1924, at 6 days of age, with the chief complaint of vomiting and refusal to nurse for three days. The abdomen was moderately distended and there were slow peristaltic waves from the left costal margin to the umbilicus. Projectile vomiting occurred two or three times daily while in the hospital.

The second entry was at the age of 3 months. The chief complaint then was constipation. Barium enema was done, this time revealing the colon to be of large caliber with an elongated dilated sigmoid loop.

In a follow-up note at the age of 4 years he was reported to be having but one bowel movement per week and that following enema. Six months later he had a complete obstruction due to fecal impaction.

The next admission was at 7½ years of age. At that time the complaints consisted of vomiting, no bowel movements without enemas, anorexia, and loss of weight. Repeated barium enema showed the colon to be dilated to three times normal size from the mid-transverse colon to the lower half of the sigmoid. Spinal anesthesia was given with 60 mg. of neocaine without any change in the colon. Bilateral lumbar sympathectomy was done on March 12, 1932, through the abdominal approach. At operation it was noted that the sigmoid and lower two-thirds of the descending colon were very large and distended with pale, grayish thickened walls. Spontaneous bowel movements occurred within the few weeks after operation. For the next four years he continued to have daily bowel movements with the use of mineral oil and cascara nightly. Fecal impaction then occurred requiring hospitalization.

Two weeks later, at the age of 12, he was again hospitalized because of volvulus of the sigmoid colon and fecal impaction. At this time a three-stage Mikulicz procedure with resection of the sigmoid colon was done. Recovery from this operation was uneventful and he was again having normal bowel movements on discharge.

One year later he was again hospitalized for fecal impaction. Barium enema at this time showed a narrowed area at the junction of the descending colon and rectum. Proximal to this point the colon was atonic and dilated excessively. The descending, transverse, and ascending colon and cecum were normal in length but abnormally wide. There was surprisingly good emptying of the bowel following defecation.

Thereafter, he was seen in the outpatient department, usually for some complaint not referable to the primary disturbance. When last seen, at the age of 17

years, he was reported to be in good health with good appetite, normal weight, and an abdomen that was flat and soft. Occasionally he had mild episodes of constipation relieved by laxatives. Thus, for five years he has had a fairly normal course regarding bowel habits.

This case was unsuccessful after a sympathectomy; it presented one of the dangers, that is, obstruction due to volvulus. It was interesting to note the change in disposition when the patient's bowels were functioning normally as contrasted to a sullen, toxic-looking chap when he had a fecal impaction.

Fig. 1 shows the x-ray study of his large bowel in 1940. While there is dilatation of the bowel, as shown, he has normal bowel habit.

Fig. 1 (Case 1).—X-ray taken Feb. 2, 1940.

CASE 2.—G. V., a female, was admitted to this hospital for the first time at the age of 3 weeks. She was vomiting frequently and had lost weight. Bowel movements were infrequent and obtained only after suppositories. Barium enema showed a spastic narrowed rectum with slightly dilated atonic colon and abnormally dilated ileum. She was admitted twice more in the next three months because of increase of vomiting and constipation. At the age of 2 months a spinal anesthesia and barium enema were done with no increase in expulsion of stool.

At the age of 6 months the vomiting again became severe and there was no stool even with milk of magnesia and mineral oil. At this time the abdominal distention was first observed and there were visible peristaltic waves. Barium enema and spinal anesthesia were repeated without beneficial results. After this admission the infant was brought to the outpatient department for colonic flushes as the home care was inadequate. Outpatient department visits became infrequent and when next seen at the age of 4½ years it was reported that she had done fairly well in the

interim with mineral oil, laxatives, and enemas. At that time barium enema showed marked dilatation of the whole bowel. Surgery was advised.

Her fifth admission was on March 1, 1939, at the age of 5 years. Following preliminary cleansing of the colon a Mikulicz procedure was done with resection of 72.5 cm. of large bowel from the sigmoid up to the mid-transverse colon. The postoperative course was uneventful. On discharge she was having spontaneous daily bowel movement. Six weeks later she returned with a fecal impaction which was removed with oil retention enema.

A barium enema at the age of 6½ years showed considerable dilatation of the distal half of the transverse colon. In the next three months she had two episodes of fecal impaction, one so severe as to cause partial obstruction.

Nearly a year elapsed before her next hospital visit which was on Sept. 7, 1942. Her mother stated that she had been very well until three weeks before entry. Bowels had moved once or twice a day without mineral oil or laxatives. Flatulence had been quite marked. In the last few weeks her appetite had been impaired and there had been no bowel movement for three days. Laxatives had been given but caused abdominal pain and vomiting. On examination there was a large firm mass which took eleven days of mineral oil by mouth and rectum and a variety of different enemas to remove. Barium enema after apparent cleansing showed an orange-sized mass in the sigmoid and some difficulty of passage of the barium through the site of previous anastomosis in addition to a dilated colon. One week after discharge another fecal impaction occurred and this had to be broken up under anesthesia and removed manually. Surgery was again advised.

Cecostomy and appendectomy were done Oct. 3, 1942, and ten days later a complete colectomy was done. At operation the large bowel from the point of previous anastomosis to the cecum and the distal three inches of the ileum was dilated and thick walled. The terminal ileum was transected and an end-to-side anastomosis with the lower sigmoid done. There was a moderately stormy postoperative course with liquid stools, moderate distention, anorexia and weight loss, occasional emesis, and colicky abdominal pain. Much of this was relieved by prostigmine but recovery was slow with much distress.

She was home three weeks when there was a recurrence of colicky abdominal pain associated with vomiting. The abdomen was very distended with tremendous peristaltic waves. It was felt that she had partial obstruction probably at the site of previous anastomosis. The condition cleared in two days in the hospital.

This patient had very poor home care. She did very well as long as she was in the hospital and away from her parents.

Case 3.—F. M., a male, was first admitted to this hospital on Sept. 11, 1940, at the age of 3 years, with the chief complaint of severe constipation and abdominal distention since infancy (see Fig. 2). His early history was interesting in that he was normal at birth and did very well for the first ten days. Vomiting then started and, four days later, severe diarrhea with profuse foul stools. In spite of various forms of treatment and many formula changes the diarrhea lasted for two weeks. During this time he lost weight so that at 1 month of age his weight was 4 pounds, or one-half of his birth weight. A soybean formula was tried and on this the diarrhea ceased and he began to gain weight. Within the next few weeks he became constipated and this progressed so that bowel movements were secured only with the use of laxatives. These were effective in producing three or four bowel movements per week for nearly two years but after that they were no longer effective and the mother resorted to enema. Meanwhile, there was progressive and marked enlargement of the abdomen.

At the time of entry the examination was not remarkable except for the huge abdomen which was doughy to palpation. On barium enema the colon was distended

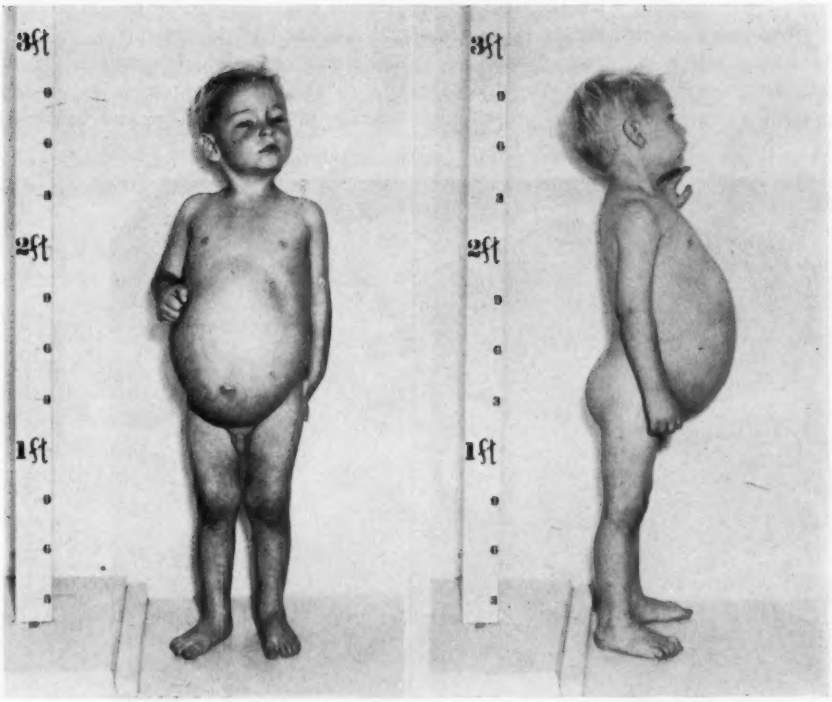

Fig. 2 (Case 3).—Taken Sept. 12, 1940, on first admission.

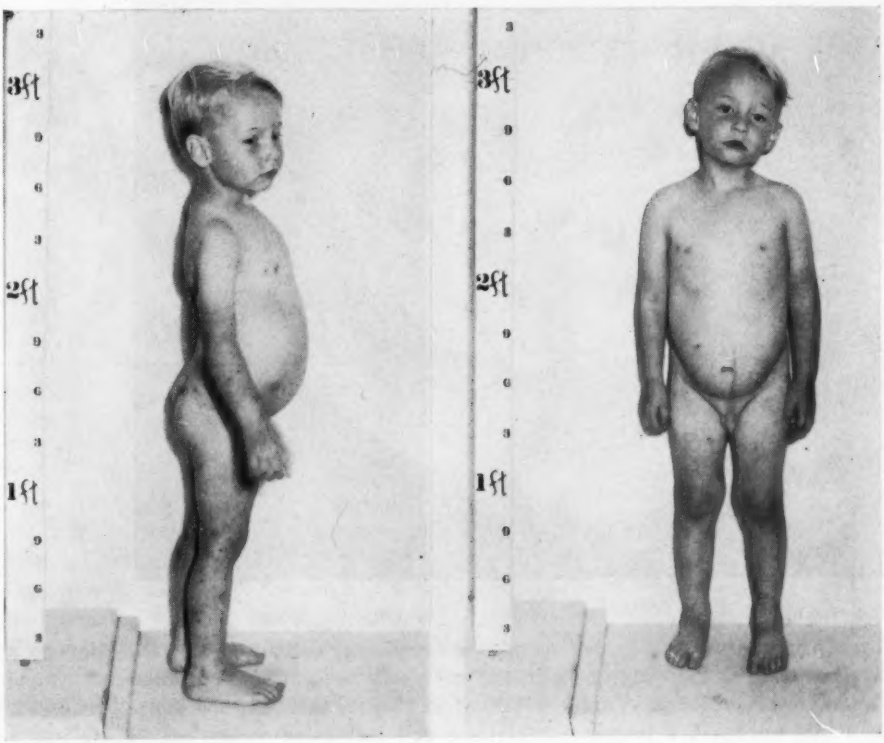

Fig. 3 (Case 3).—Taken July 10, 1941, nine months after sympathectomy.

throughout its entirety with the descending portion dilated up to 10 cm. in diameter. After four hours 90 per cent of the barium still remained in the colon.

He was given a six weeks' trial of medical treatment which consisted of non-residue diet, enema, vitamin B, physiotherapy to the abdominal muscles, mecholyl up to 0.2 Gm. twice a day, plus prostigmine bromide 0.015 Gm. daily, and finally syn-

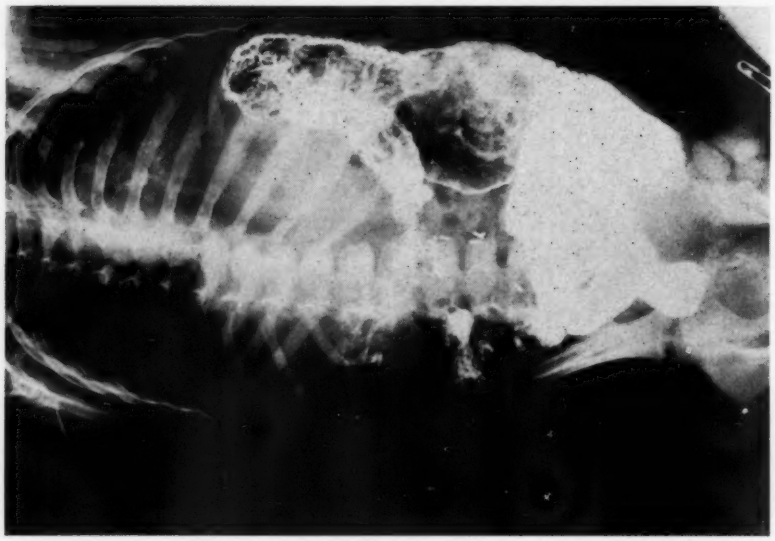

Fig. 5.

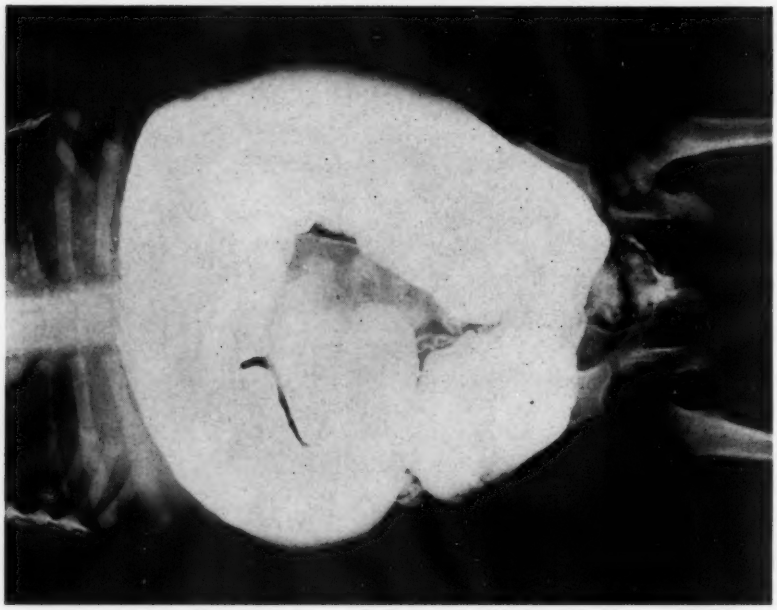

Fig. 4.

Fig. 4 (Case 3).—Barium enema nine months after sympathectomy.
Fig. 5 (Case 3).—Barium enema done Nov. 4, 1941, thirteen months after sympathectomy and after one year of medical treatment.

tropan 0.5 Gm. twice a day, but no spontaneous bowel movement occurred although a severe reaction to the drugs necessitated emergency use of atropine. Bilateral sympathectomy was decided upon and carried out on Nov. 5, 1940. At operation through the abdominal approach a tremendous sigmoid and left colon were seen. There was a change in the bowel wall at about the junction of the middle of the transverse colon

and at the middle sigmoid area. The bowel between was soggy, thick walled, and rather lifeless. The right colon appeared normal, though somewhat dilated. He made an uneventful recovery, though without spontaneous bowel movement.

Eight months later he was readmitted. He had gained weight and felt well but bowel movements were not normal, although occasionally he had a small one. A barium enema was repeated giving mecholyl and prostigmine but there was no increase in visible peristalsis. However, he was discharged on mecholyl 0.1 Gm. twice daily.

He was again hospitalized two months later, Sept. 29, 1941. The interval history was that he had been having bowel movements almost daily with the mecholyl though suppositories were frequently necessary to initiate them. When the supply of mecholyl was exhausted three weeks before re-entry, constipation recurred. In spite of resumption of mecholyl in doses up to 0.3 Gm. twice daily, there were no spontaneous bowel movements.

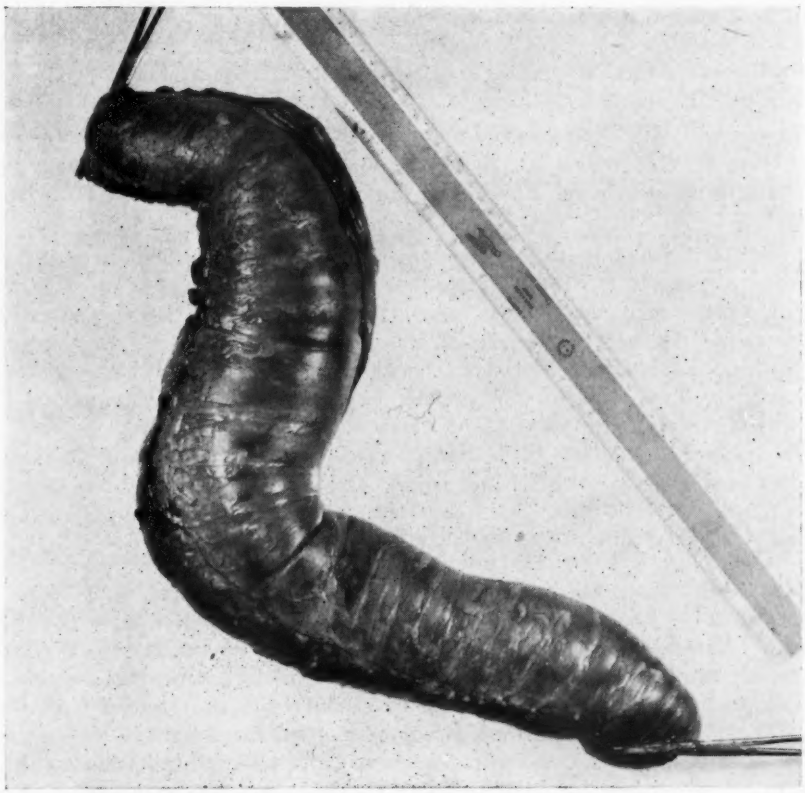

Fig. 6 (Case 3).—Resected specimen.

Since the family lived at a great distance from the hospital and were often isolated during the winter for days at a time, it was felt that with the risk of volvulus not remote, a colon resection should be undertaken. Therefore, a preliminary cecostomy and appendectomy was done Nov. 10, 1941.

On Dec. 3, 1941, at the age of 4 years and 3 months, a left colon resection was done with an end-to-end anastomosis; 63 cm. of the colon were removed (see Fig. 6). Recovery was uneventful and was followed by daily spontaneous bowel movements. Fourteen months later, he was reported as having normal daily bowel movements.

CASE 4.—D. S., a male, was first admitted to this hospital on March 13, 1942, at the age of 3 years and 3 months. His chief complaints were abdominal distention since birth and constipation since the age of 6 months. Birth was normal but on the second day he began vomiting. This was projectile and stained yellow green. As this continued, a diagnosis of pyloric stenosis was made and an operation performed elsewhere on the eleventh day. Following the operation there was no further vomiting and stools were reported normal. However, on the fifth day abdominal distention became so marked that the sutures broke and the incision had to be repaired. The distention continued and considerable gas was passed by rectum but the infant seemed well otherwise.

At about 6 months of age constipation was first noted and this progressed as did the distention. Occasionally periods of diarrhea would occur. Early, mineral oil and laxatives were effective in control of constipation, but by 1 year of age only enemas produced passage of stool.

Examination was normal except for the abdominal findings of moderate distention especially of the left lower quadrant where peristaltic waves were visible and hard fecal masses palpable. Barium enema showed mild dilatation of the sigmoid. This was repeated under spinal anesthesia, showing that the colon emptied into the sigmoid which in turn was unable to discharge its contents into the rectum and so became more dilated.

He was treated with flushes and then mecholyl 0.1 Gm. twice daily. Later prostigmine bromide 0.015 was added. He developed a reaction to mecholyl after nine days, but no spontaneous bowel movement. He was also given vitamin B and colonic flushes.

Since the diseased portion of the bowel seemed so well localized, resection was advised. On April 14, 1942, an appendectomy and cecostomy were done and on May 1, 1942, a resection of the sigmoid loop (15 cm. in length) and end-to-end anastomosis. At surgery the sigmoid was found to be three or four times normal size with a thickened wall. The sigmoid with a margin of normal colon on either side was resected. Two grams of sulfanilamide were left in the abdominal cavity. Recovery was uneventful with normal bowel movements before discharge.

He was seen at intervals in the outpatient department during the next six months. He was having daily normal bowel movements and if occasionally one day missed, mineral oil corrected this. The only complaint was occasional soiling but this seemed a behavior situation rather than true incontinence.

CASE 5.—F. N., a female, was first admitted to this hospital on May 20, 1942, at the age of 4 years, with the chief complaint of constipation since the age of 5 months. Mineral oil and molasses given daily relieved the constipation for the succeeding five months. From the age of 10 months to 4 years enemas were necessary to produce a bowel movement. A low residue diet and vitamin B gave no relief. Mecholyl has been given in the few weeks preceding admission without results.

On admission the patient was very well developed and nourished. The only abnormal finding was the large protuberant abdomen which was doughy to palpation with large fecal masses palpable on the left side. Barium enema showed moderate dilatation of the sigmoid region. Colonic flushes were given to cleanse the colon and then the patient was given mecholyl 0.05 Gm. three times a day for ten days. Since the lesion was apparently well localized and failed to respond to medical treatment, surgery was decided upon. An appendectomy and cecostomy were done on June 3, 1942, and 13 cm. of sigmoid were resected on June 23, 1942. The large bowel appeared to be normal except in the region of the sigmoid where it was easy to demonstrate the difference between the thick-walled soggy sigmoid and the normal bowel, both distal and proximal.

The postoperative course was uneventful and a normal bowel movement occurred

on the fourth postoperative day. Cecostomy was closed on the seventeenth postoperative day.

A follow-up on Feb. 1, 1943, showed a gain of five pounds, good appetite, and two to three formed stools daily without any medication.

CASE 6.—J. W., a male, was admitted to this hospital on July 17, 1942, for the first time, at the age of 6½ years. His early history was noteworthy in that he began having projectile vomiting the first few days after birth and this continued until the third month. Abnormal stools, infrequent but copious, were noted during the nursery period. Distention did not appear until the sixth week. Bowel movements occurred once to twice a week during the first two years in spite of the use of laxatives, vitamin B, and mineral oil. Colonic flushes were given every other day from the age of 2 years on.

On examination the patient was normal except for the tremendously enlarged abdomen with thin walls and easily palpable colon.

Treatment consisted of the routine cleansing procedure plus low residue diet and vitamin B. He was started on mecholyl and reached a dosage of 0.2 Gm. twice a day and then prostigmine bromide 0.015 Gm. was added with each dose of mecholyl. On this regime he had one single very small spontaneous bowel movement and no more. Barium enema under spinal anesthesia showed no change in the tremendously dilated colon.

Cecostomy as a preliminary to resection was done on August 15, 1942, and 90 cm. of the left colon were resected on September 2, with an end-to-end anastomosis. The diameter of the resected colon was 13.7 cm. There were enlarged nodes in the mesentery of both large and small bowel. The line of demarcation between diseased and normal bowel was quite distinct distally but less so proximally. Two grams of sulfanilamide were left in the peritoneal cavity and 1 Gm. in the wound. His postoperative course was somewhat stormy with vomiting, abdominal distention, and low-grade fever. However, the cecostomy was finally closed three weeks later and about that time he began to have almost daily bowel movements. He was discharged on Oct. 10, 1942.

He was readmitted two days later because of vomiting, abdominal pain, and temperature of 39° C. On examination he was dehydrated and obviously very ill. Abnormal findings on examination were a moderately injected pharynx and distended abdomen, which was tympanitic. There was slight para-umbilical tenderness but no rigidity. Rectal examination was not abnormal. The white blood count was 13,700 with 74 per cent polymorphonuclears. Plain film of the abdomen showed huge dilatation of the colon which was filled with gas and showed fluid levels. Thin barium showed no obstruction.

The patient was treated with intravenous fluids and Wangensteen suction. As there was no real improvement after two days of this therapy, an exploratory laparotomy was done. No mechanical obstruction was found. There was a very large group of nodes in the mesentery of the small bowel. The appendix was found to be very large and firm but not markedly inflamed; it was removed without difficulty. The site of the previous anastomosis was patent. The pathologic report was acute appendicitis with acute mesenteric adenitis.

Again the postoperative course was somewhat stormy with episodes of vomiting and distention. Transfusions and intravenous fluids were given as supportive treatment. Mecholyl and prostigmine were started on the ninth day. The following day he was given a large dose of prostigmine by error and shortly after this there was an emesis of 700 to 800 c.c. and a large stool of over 800 c.c. both formed and liquid. Subsequently his appetite returned, he gained weight, and had spontaneous daily stools. Report from his mother in February, 1943, stated that he was gaining weight, had a good appetite, and was having normal daily bowel movements.

DISCUSSION

It is our plan now, in these early cases, to attempt to control the bowel habit by diet, vitamin B, mecholyl, or syntropan and colonic flushes if necessary; and if this is not adequate, to give a spinal anesthetic in the fluoroscopic room so as to watch the response of the colon. If there is no response from the anesthetic and the medical regime is inadequate, then the involved segments should be resected in two stages.

While mecholyl is a useful drug it is toxic and the dosage must be watched very carefully. We feel it might be well to have these patients continue on small doses in order to increase the bowel tone after discharge from the hospital.

SUMMARY

This is a report of six cases of Hirschsprung's disease in patients between the ages of 3½ and 12 years, who had resection of the involved segments, without a death. This is partially luck but the close coooperation between the two departments is most important.

The results have been satisfactory in five. The patient in Case 2, who required a total colectomy, has not done so well.

In our hands sympathectomy or medical treatment alone or together has not been satisfactory.

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POSTCHOLECYSTECTOMY RUPTURE OF THE COMMON BILE DUCT

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A REVIEW of the literature indicates that rupture of the common bile duct following cholecystectomy has been rarely described. In 1935, Newburger collected nine such cases proved at operation or necropsy and reported one of his own. All patients were women, their ages varying from 25 to 59 years. All had undergone cholecystectomy and choledochostomy except one, who had had only cholecystectomy. The point of rupture was the tied cystic duct stump in five instances, the point of drainage of the common duct in three instances, and elsewhere in the common duct in two instances. Stones were present in the common duct in seven cases, and were absent in the remaining three instances. The time of rupture following cholecystectomy varied widely, the shortest period being twelve days, the longest three and one-half years. In one case (Wolfson and Levine), a cholecystectomy had been performed twenty-five years previous to choledochostomy. Fifty-five days after the latter operation there was rupture of the common duct and bile peritonitis. This patient recovered following T-tube drainage of the common duct and had common duct stones removed a few months later. In all of the other patients referred to above death followed drainage of the extra-hepatic biliary tract instituted for the rupture.

Perforation, not the result of pressure from stone, of a diverticulum of the choledochus just below the cystic duct was described by Wernsdörfer in a man aged 40 years. Small stones were evacuated and the choledochus drained with a T tube; recovery ensued.

Recently Newell reported the instance of bile accumulation in the abdomen where at laparotomy no gross perforation of the extrahepatic biliary ducts or of the gall bladder was demonstrable, although the wall of the choledochus was edematous and infiltrated with bile-stained fluid, suggesting an extravasation from a minute or even healed perforation. This author cites Bailey's patient in whom the perforation was discovered only at necropsy and found to be on the posterior aspect of the junction of cystic and common ducts. Vale's case is also cited, in which there was extravasation of bile in the peritoneal cavity without gross evidence of perforation. Recovery followed drainage.

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In Reich's patient, a man aged 73 years, laparotomy revealed an extensive accumulation of bile-stained fluid in the peritoneal cavity and there was a perforation in the common hepatic duct. No concretions were present. Death ensued a few hours after laparotomy and necropsy revealed cirrhosis of the liver. The large extrahepatic bile ducts were not markedly diseased and the gall bladder was small and contracted.

Two additional instances of perforation of the common bile duct are cited below.

CASE 1.—M. C. (No. 284550), a woman aged 67 years, was admitted to Billings Hospital May 7, 1942, complaining of severe attacks of cholecystitis in January, 1941, with marked jaundice. In another institution, a cholecystostomy was performed in February, 1941, with evacuation of many concretions from the gall bladder and common duct. Following recurrence of another severe attack, a cholecystectomy was performed in April, 1941, and according to the history obtained a concretion was also removed from a diverticulum (?) of the common duct above the head of the pancreas. Since the second operation, the patient's condition was good until three days prior to the present admission, when a severe epigastric pain developed that radiated to the interscapular region. The next day icterus was apparent and the severe pain with nausea and vomiting persisted. The patient was brought to the hospital in an ambulance and appeared acutely ill. Temperature was 101° F. (rectal); W.B.C., 18,650; Icteric index, 19.5; N.P.N., 111 mg. per cent; pulse, 72; B.P., 100/70. General abdominal tenderness was noted with no rigidity or palpable masses; some distension was present. Parenteral glucose and saline solutions were administered and the next day the patient felt slightly improved. During the next four days the temperature rose gradually to 103° F. (rectal). The physical findings did not change appreciably during this period except for increased intensity of the icterus which then appeared to clear, the icteric index reaching 35 and then falling to 14 on the sixth day; the W.B.C. rose to 31,000. At 4:00 A.M. the morning of the seventh day, the patient suddenly expired. Necropsy revealed generalized acute bile peritonitis secondary to a small perforation 1 mm. in diameter in the common bile duct which was situated 3.5 cm. below the cystic duct stump. The common bile duct was markedly distended and at a little distance below the perforation contained a single faceted cholesterol stone 1.4 cm. in diameter. At the level of the stone the common duct wall was thicker than elsewhere. The diverticulum of the common duct said to have been observed at the last operation was not found.

CASE 2.—M. S., a woman aged 72 years was admitted to Billings Hospital Dec. 22, 1942. Since 1939, there had been attacks of right upper quadrant pain radiating to the back and shoulders, with nausea, vomiting, and transitory icterus. Cholecystectomy was done in 1941, and following this there was freedom from attacks. Three days prior to the present admission severe pain developed in the right upper quadrant and radiated to the left shoulder. Nausea and vomiting were frequent and icterus developed. On physical examination there was diffuse abdominal tenderness with muscle spasm in the right upper quadrant. Temperature was 102.8° F. (rectal); W.B.C., 19,800; Icteric index, 47; B.P., 130/70; pulse, 120. During the next three days the general asthenic condition of the patient improved slightly, nothing having been permitted by mouth and a total of 3000 c.c. of dextrose and saline solution being given daily parenterally. At the end of this period the abdominal rigidity was sharply localized to the upper right quadrant where a deep abscess seemed to have formed (fluctuation). The remainder of the abdomen was

flaccid and only slightly tender. Laparotomy was performed by excision of the old upper right rectus incision scar, and the deeper layers of the abdominal wall were observed to be edematous and bile stained. When the peritoneum was incised dark green, thick purulent fluid escaped from a cavity lined by fibrinous exudate. This cavity was observed to be a large pocket below the right lobe of the liver anterior to the porta hepatis. When all purulent material had been cleaned out, the common duct, about 2 cm. in diameter, was observed at the bottom of the pocket, and at a point about 2 cm. above the upper margin of the duodenal curvature there was an oval perforation about 1.5 cm. in diameter. The index finger was inserted into the common duct in both directions and distally behind the duodenum an oval concretion about 1.5 cm. in diameter was palpated. This was lifted out through the perforation in the common duct. Probing in both directions

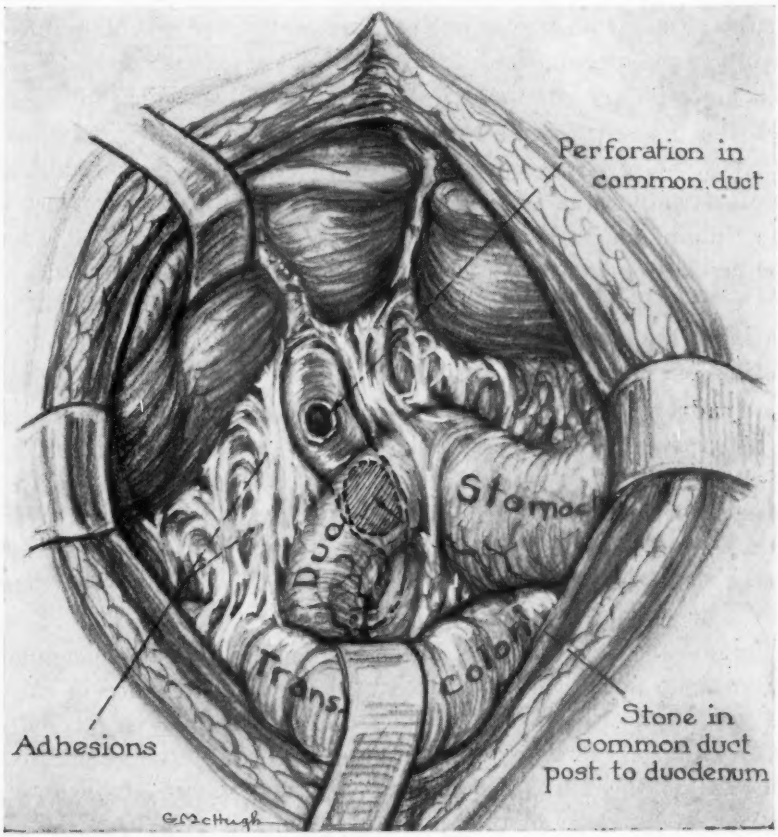

Fig. 1.—Showing findings at laparotomy in Case 2. Large pocket exposed through incision of abdominal wall was filled with bile and purulent exudate; large oval perforation was present in common duct. Concretion in lower common duct was somewhat impacted in position shown. Findings suggest rupture due to hydrostatic pressure above concretion. Recovery followed stormy convalescence.

failed to bring up other stones. A probe was passed into the duodenum via the common duct and ampulla without encountering obstruction. A catheter was inserted into the perforation and the latter closed by interrupted sutures about it. There was no visible evidence of cystic duct stump. Penrose drains were inserted into the depths of the large pocket and the abdominal wound closed. Final diagnosis: Localized upper abdominal bile peritonitis secondary to ruptured common duct,

choledocholithiasis. After a convalescence characterized by periods of marked asthenia and mental disorientation, the patient's icterus had cleared by the thirty-seventh postoperative day and stools contained bile. The small biliary fistula healed. The general condition improved markedly, and the patient was discharged from the hospital. Three months after the operation, the patient was well.

DISCUSSION

The cause of rupture of the common duct has been variously stated as due to one or a combination of factors which include: (a) increased intraluminal pressure from obstruction below the point of rupture, (b) necrosis of a portion of the common duct wall secondary to thrombosis of mural vessels, (c) necrosis of the duct wall secondary to pressure from impacted stone, (d) infection, (e) slough of the cystic duct stump, (f) rupture of a weak segment of duct wall, such a vulnerable point resulting from common duct drainage. Where extensive changes in the extrahepatic biliary duct walls are not present, and in the absence of stones, the pathogenesis of rupture is obscure. Needless to emphasize again, postcholecystectomy rupture of the common duct is another of the unfortunate sequelae of overlooked common or hepatic duct stones at the time of cholecystectomy. It is of interest to note that in both of the cases reported above the perforations in the common duct were *above* a large stone, and that judged from necropsy and findings at operation these perforations could hardly be ascribed to direct pressure necrosis from the concretions.

The syndrome of upper abdominal pain, becoming quite severe, upper and later general abdominal tenderness and rigidity, elevation in temperature, marked leucocytosis, rapid pulse, varying degrees of general collapse and icterus (after a few days) in a patient who previously has undergone cholecystectomy for cholelithiasis and cholecystitis should strongly suggest perforation of the common bile duct with extravasation of bile and bile peritonitis.

Differential diagnosis from biliary colic due only to common duct stone or stone in the ampulla should not be difficult since in the latter event the clinical evidence of peritonitis will not be present, and general collapse will not have developed. Differential diagnosis from carcinoma of the ampulla or head of the pancreas will be readily apparent also, because of the absence of evidence of peritonitis. Severe diffuse cholangeitis of sudden onset might afford some early difficulty in differentiation, but as the hours pass, lack of evidence of peritonitis will preclude the diagnosis of ruptured common duct.

The almost certain fatal outcome of this condition if laparotomy is not performed justifies laparotomy at the earliest moment when the diagnosis appears probable. Evacuation of the extravasated bile, drainage of the upper abdomen, and drainage of the common duct will afford the only opportunity for survival. While in the recorded experience the mortality following this procedure under these circum-

stances has been very high, it would, nevertheless, appear to be primarily the mortality of the disease. A more general appreciation of this late complication of cholecystectomy for biliary lithiasis might entail earlier operation with possibly a greater incidence of survival.

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MANAGEMENT OF THE APPENDICAL STUMP

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THERE are four reasons why this study was undertaken: (1) In spite of the fact that fifty-nine years have passed since Krönlein[1] in 1884, performed the first appendectomy, there is still no generally accepted technique for the management of the appendical stump. (2) Severe complications due to massive leaking of abscess of fecal material at the stump area are still being reported in the surgical literature and it is quite likely that this catastrophe occurs much more often than is indicated by these reports. (3) The occasional stormy postoperative course of an interval or incidental appendectomy and the occasional finding of many unexpected adhesions in the right lower quadrant when the abdomen is reopened, may well be due to slight unrecognized leaking of the stump area after the previous appendectomy. (4) Probably the real reason for the study lies in the fact that the authors, after trying most of the accepted methods of handling the appendical stump, were never completely satisfied with any method which they tried.

Eleven years after the first appendectomy, Dawbarn,[2] in 1895, mentioned eleven different methods of treating the appendical stump and then described a new method of his own. It is interesting to consider some of the methods that Dawbarn mentioned. They include amputation of the appendix flush with the cecum and closure of the hole by one or two rows of Lembert sutures; ligation and cauterization of the stump with the cauterization being performed either before or after ligation; ligation, cauterization, and inversion of the stump by Lembert sutures; cauterization of an unligated stump with inversion beneath two rows of Lembert sutures; inversion of a tied, cauterized, half-inch long stump concealing the suture line under omental or mesenteric peritoneum; inverting the entire unopened appendix into the cecum; amputation between clamps leaving the clamp on the stump for a day or two; and finally, doing nothing to the appendix if its removal seemed likely to spread infection.

The plan advocated by Dawbarn called for a purse-string suture one-fourth of an inch from the appendix, the appendix divided leaving a stump never shorter than one-half an inch, the lumen of the appendix to be stretched by the introduction of a pair of closed mouse-tooth forceps through the appendix into the lumen of the cecum "then gently opening the blades—thereby any stricture, from swelling or plastic deposit, will be stretched." Lastly, the untied stump of the appendix

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was to be invaginated into the cecum as the purse-string suture was tightened and tied.

By 1904, Seelig[3] was able to state that "in general the methods of treating the stump of the appendix may be grouped under three heads, as follows (Fig. 1, *I, II,* and *III*).

"(a) Ligation of the base of the appendix, ablation of the organ distally to the ligatures, and inversion of the stump by means of Lembert sutures passed through the peritoneum of the cecum. In these cases the appendical stump is inverted into the wall of the cecum.

"(b) Ablation of the organ without previous ligature of its base, and inversion of the stump into the lumen of the cecum; Lembert sutures over the site of inversion.

"(c) Simple ligation, ablation of the organ distally to the ligature, and cauterization of the stump. The disinfected stump is dropped back into the peritoneal cavity."

In 1937, Ochsner and Lilly[4] reviewed the question from the standpoint of the same three basic methods: (1) simple ligation of stump; (2) ligation and inversion of the stump into the cecal wall; and (3) inversion of the unligated stump into the lumen of the cecum. Their experience with three instances of stump leakage following the first two methods led them to consider inversion of the unligated stump the method of choice.

There are two objections to the simple "tie and drop" method of handling the appendical stump. The objection most often mentioned is the absence of serosa-to-serosa apposition when the appendix is ligated with or without preliminary crushing. If the tight tie or crushing severs the mucosa and the pulpy lymphoid tissue, the tie then brings submucosa to submucosa and not serosa to serosa. While this is important, it is not as important as the other objection to this simple ligation technique. This second objection lies in the fact that the stump of the appendix not only sloughs distal to the tie but also sloughs at the point of the tie. In fact no healing takes place until this slough is removed. If a dog's abdomen is opened four or five days after its appendix has been tied with 0 chromic catgut and the carbolized stump dropped back into the abdominal cavity, the operator will see a mass of fibrinous adhesions joining ileum or omentum to the stump area. If these are carefully separated, either an opening into the cecum will be found or the site of the appendical stump will be closed by a very thin layer that looks like a spider web. If, on the fourth or fifth postoperative day, the adhesions about the stump are not separated but the cecum is squeezed gently, fecal material can be seen escaping from the insecurely healed stump. This finding was noted in the five animals treated by the simple "tie and drop" method. It seems that from the moment the appendix is tied a race is started between the protective adhesions which tend to cover and seal off the necrosing stump and the anemic necrosis

Fig. 1.—*I*, Simple ligation of stump; *II*, inversion of tied stump; *III*, inversion of unligated stump; *IV*, inversion of small stump made possible by the use of a catgut pursestring instead of a tie about the base of the appendix.

at the point of the tie which tends to slough into the lumen of the cecum. It may be that the mucosa, severed by the tie or crushing, grows over the opening in the cecal wall and saves the day, but the cecal wall cannot start healing until it first sloughs through. This means that for a few days there is a distinctly weak area in the cecal wall. In the experimental animals examined three weeks after operation only a few adhesions were evident but the cecal wall showed no evidence of weakness. That the race is usually won by the defense mechanisms is attested to by the fact that so many appendectomies are successfully handled by this technique. However, there is little doubt but that there is a period of great danger at some point probably about the third or fourth day, when the appendical stump is partly sloughed away and when the defenses are still fibrinous. Marked distention, straining, or a "high" enema during this period could well cause the filmy covering of the stump to give way, allowing either a small or possibly a large cecal leak. This series of events might explain the occasional unexpected thicket of adhesions about the cecum and ileum in a case that had had an incidental appendectomy or interval appendectomy but a stormy postoperative course.

The inversion of the unligated stump method produces the highly desirable serosa-to-serosa apposition of the stump which is turned into the cecum. It also produces no pocket in the cecal wall as the end of the stump is pushed into the lumen of the cecum. Four dogs were operated upon by this technique. On the fourth or fifth day, reoperation showed the best healing of any of the experiments with little or no adhesions on the outside and but slight sloughing evident on the inside. If this inversion could be made safely there would be no question about this being the method of choice. The difficulty lies in the anatomic fact that the wall of the appendix is so thick in comparison with the small diameter of its lumen. This state of affairs makes complete inversion of the untied appendical stump into the cecum difficult and at times impossible. It should be remembered that Dawbarn, the originator of this technique, advised stretching the lumen of the appendix with a forceps introduced through the stump into the cecum before attempting inversion of the stump. Many ingenious methods[4-7] of inverting the untied appendical stump into the cecal lumen have been described but they have two objectionable features. One is the possibility that the unligated stump is not inverted, but merely pushed down into the cecal wall, and the other, the danger of soiling the field as the unligated stump is forced in on itself into the lumen of the cecum. If an assistant squeezes the cecum too tightly, if a narrow forceps or clamp does not completely close the end of the stump as it is being inverted, or if the purse-string suture should break before the stump was completely turned in on itself, soiling is possible. The question of hemorrhage from the unligated appendical artery has often been mentioned as a danger

of this technique. This danger seems more theoretical than real. It is recognized that a trained operating team can invert the unligated appendix stump with no soiling, but the technique can become difficult and if the members of the team are unfamiliar with the dangers of the technique, soiling is possible. For this reason inversion of the unligated stump of the appendix does not seem to be the safest method of handling this problem.

Inversion of the tied appendical stump avoids the danger of soiling during inversion but carries with it the objectionable feature of producing a pocket in the cecal wall, a pocket that contains the necrotic appendical stump caught between the catgut tie below and the silk or cotton pure string above. Using eight dogs, appendectomy was done by this technique; the tie was of 00 chromic catgut and the purse string of quilting cotton. Reoperation on the fourth or fifth day revealed adhesions about the stump area that were more abundant than those found after inversion of the unligated stump technique but much less than was found after the simple ligation experiments. In no instance could fecal material be squeezed out of the imperfectly healed stump area. Four animals were reoperated upon on the twentieth postoperative day. The only noteworthy finding at that time was the reduction in size of the inverted stump when viewed from within the cecum. The stump had probably sloughed off and drained into the cecum because all that was left was a small nubbin 7 mm. in diameter and projecting into the lumen about 1 or 2 mm. Microscopic examination of the stump areas removed on the fourth postoperative day showed necrotic tissue and abscess formation in every instance but there was little spread of the inflammatory reaction into the cecal wall that formed the sides of the pocket. This tends to discredit the objection to a purse-string suture on the grounds that it devitalizes the cecal wall and makes the wall subject to invasion of infecting agents. The observation that the intact serosa checks the spread of inflammation into the cecal wall further suggests that the serosa of the appendical stump and cecal wall should be left intact and not crushed nor incised and crushed before ligation, if the stump is to be inverted. Some slides showed the pocket abscess extending dangerously close to the cotton purse-string suture. It seemed that a second purse string which would turn in a little more serosa would add materially to the safety of the procedure.

It was evident that here again a race was in progress. A race between the holding properties of the purse string above and the catgut tie below, with the pace determined by the enlarging abscess between the two, since it was very evident from these specimens and sections that the size of the inverted stump determines the size of the resulting abscess. It follows, therefore, that any reduction in the size of the inverted stump would reduce the size of the cecal pocket abscess. The smaller abscess should slow the tempo of the race and by slowing the race, favor the cotton

purse string which can stand time better than can the catgut tie. If an operator tries to achieve this end by cutting closer and closer to a catgut tie, the tie is likely to be pulled off during the subsequent carbolization of the stump. If, however, instead of a tie, a purse-string suture of catgut is placed at the very base of the appendix and tied tightly, the appendix can be cut off flush with this suture (Fig. 1, *IV*). This reduces to a minimum the amount of tissue turned into the cecal wall and thus should tend to reduce the size of the cecal wall abscess.

Experiments were carried out on eight dogs employing this double purse string rather than the catgut tie and cotton purse string technique (Fig. 1, *IV*). On the fourth or fifth day, reoperation revealed little or no reaction about the site of inversion. It looked about the same as the stump area following the inversion of an unligated stump. This means there was less reaction than was found after the ligation and inversion technique and, of course, much less reaction than found after the "tie and drop" technique. In four instances, sections made through the cecal pocket area found following the inversion of the small stump showed a subacute inflammatory reaction rather than an abscess (Fig. 2). In some sections the reaction was certainly not enough to be called an abscess since it showed only granulation tissue. Four animals were reoperated upon on the twentieth postoperative day. The outer surface of the cecum showed very few adhesions and the inner surface showed only a tiny elevated area 4 mm. in diameter.

This technique is applied to the human appendix in the following manner. A Kelly clamp is applied to the distal end of the meso-appendix, the peritoneum of the lateral side of the meso-appendix is incised if the meso-appendix is thick, or if the appendix is angulated in its mid-portion. This allows the entire appendix to be delivered from the depths of the wound and also allows the operator to see and doubly clamp only the vessels of the meso-appendix. After the vessels are divided the clamps on the mesoappendix are replaced by silk or cotton ties and usually a suture is tied about a small artery found in the angle between the appendix and the part of the cecal wall covered by the meso-appendix. Division of this artery mobilizes the cecum in the region of the base of the appendix and also reduces the likelihood of hematoma formation during the placing of the various purse-string sutures. The first purse string is placed exactly at the base of the appendix and is of 00 plain or 00 chromic catgut on a straight intestinal needle. If the base of the appendix is deep in the wound due to a fixed cecum, this purse string can best be placed with very fine curved French or split-eye needle. The bites of the catgut purse string should be as small as possible and should include only the serosa and part of the muscularis of the appendix. Usually only four or five bites need be taken in placing this purse string. As soon as the purse string is placed it is tied tightly and the ends of the suture cut. The usual purse string of

cotton or medium silk is next placed in the cecal wall about the base of the appendix. It is desirable, however, to place this purse string closer to the base of the appendix than would be possible if a large stump were to be inverted. An Ochsner clamp is then placed immediately

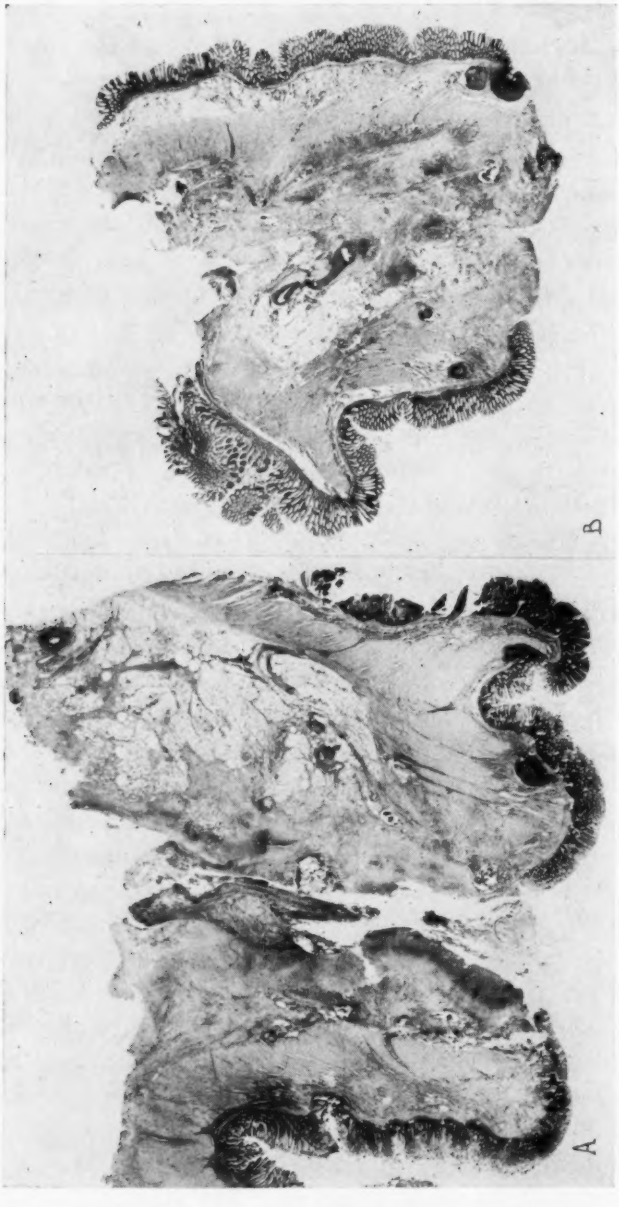

Fig. 2.—*A*, Section through stump area taken on fourth postoperative day following inversion of tied carbolized stump. *B*, Section through stump area taken on fourth postoperative day following inversion of smaller stump made possible by the double purse-string technique.

distal to the tied catgut purse-string suture. After it has crushed the appendix for a moment or so it is removed and a small straight clamp is applied to the distal part of the groove left by the heavy Ochsner clamp and the appendix is then amputated as close to the catgut purse-string suture as possible. This method of amputating the appendix

prevents soiling as the amputation is carried out through the dry crushed groove left by the Ochsner clamp; it also results in a minimal amount of appendical stump left to be turned in. After the small flat stump has been treated with phenol and alcohol, it is easily inverted by the cotton purse-string suture in the cecal wall. The procedure is completed by the insertion of either a mattress suture or a small three or four bite purse-string suture of cotton that picks up only a seromuscular bite and tends to turn in a little more peritoneum at the critical point of stump inversion.

An objection might be raised to the many stitches taken in the cecum by this triple purse-string method of handling the appendical stump. However, the stitches of the catgut purse string are quite safe because they are placed in the serosa and muscularis of the relatively thick-walled appendix. The outermost suture is safe because it also engages only the serosa and muscularis. The middle cotton or silk purse string which engages a few fibers of the submucosa is a dangerous suture if it is placed with a large needle and especially if this needle is a curved needle held in a needle holder. If, however, a fine straight needle such as a No. 8 Warwick Castle Milliner's needle and quilting cotton or medium silk thread is used, it is possible to place this middle purse-string suture safely. This view is supported by the fact that when the needle and what was left of the cotton thread after the purse string had been tied were cultured in fifteen instances and there were no positive cultures.

CONCLUSIONS

The fate of the appendical stump has been studied in the dog. Apparently, the size of the tied inverted stump determines the size of the resulting cecal pocket abscess which is the chief objection to the inversion of a tied appendical stump. The substitution of a catgut purse string for the usual catgut tie about the base of the appendix allows amputation of the appendix flush with this catgut purse-string suture, thus reducing to a minimum the amount of appendical stump to be inverted.

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

STUDIES OF THE CIRCULATION IN CLINICAL SHOCK

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INTRODUCTION

THE investigation reported in this and subsequent papers is a study of the circulation in various types of injury as met with in the admitting emergency service of Bellevue Hospital, New York. A considerable proportion of these cases showed in varying degree the manifestations of shock, and the primary purpose of the work has been to describe the circulatory changes in shock in human subjects.

The physiologic measurements have been chosen so as to make this description of the circulation as comprehensive as possible. Specifically, the major functions of the general systemic circulation which have been measured in each subject are:

1. Intravascular pressures, in femoral artery, median basilic vein, and the right auricle.
2. Plasma volume, by the dye technique of Gregersen; red cell and total blood volume (using hematocrit values); plasma protein.
3. Cardiac output, by "direct Fick" technique.
4. Pulmonary ventilation, respiratory gas exchange.

In addition, the circulation through one organ, the kidneys, has been measured in a number of cases, by the clearance techniques of Smith.

Of these measurements, the intra-auricular pressure and the "direct Fick" cardiac output, achieved through direct catheterization of the right auricle, and the renal clearances have not previously been reported in the investigation of traumatic shock in man.

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development, and Columbia University, with the collaboration of New York University. Additional support for the research was provided by the Commonwealth Fund and the Josiah Macy Foundation.

The clinical material that has been available to us, while varied, has also been in many respects quite limited. We have seen a number of cases of skeletal trauma, especially multiple fractures, several head injuries, burns, hemorrhages, and abdominal injuries. On the other hand, chest injuries have been few and we have had but one case of gunshot wound, no stab wounds, or wounds with extensive loss of muscle substance. Also, most cases were seen soon after injury so that the effects of exposure, dehydration, etc. were rarely encountered. The age distribution was wide; while many patients were in the older age groups, a number were young and had been in excellent physical condition before injury. Acute alcoholism was a complicating factor in several instances.

In the presentation of data, consideration will be given both to combined or average results in various types of injury, and to particular results in special individual cases. Average values show trends and thus define the general pattern of the condition that is under study. The exceptional case is often blotted out in the average. We believe that our techniques are both sufficiently comprehensive and sufficiently reliable so that the data of the single case study are significant. Individual responses to injury, though they may be exceptional within small groups of cases such as have been available to us in the present investigation, may be of great importance from the point of view of the mechanism of shock.

For example, it is important to know that, in a group of cases, there is a large decrease in the average figure for circulating blood volume. It is of equal importance to know whether, in specific instances, the state of shock *can* develop *without* extensive loss of blood volume.

The present paper will include the following:

1. Description of procedure and of the various methods of measurement employed, with critical comments concerning some of these methods.

2. Description of the state of circulation in various types of injury, both with and without shock, on the basis of average results in thirty-six cases.

3. Changes in the circulation occurring during recovery from shock, on the basis of average figures in six cases.

4. The state of the renal circulation in relation to shock.

In subsequent papers, a number of individual cases will be described, illustrating not only particular states of shock, but also various forms of progressive change occurring during the periods of observation, the latter lasting sometimes a few hours, sometimes several days. Data will also be presented showing the changes in blood volume produced by administration of fluids, blood, plasma, and saline; serum electrolytes in certain cases of shock; types of arterial and of right ventricular pressure curves obtained by an optical registration method; additional observations on renal clearances; and the effects of certain drugs.

The research has been in many respects a cooperative effort. Much of the original plan of the work was due to Lt. Col. Frank B. Berry, at that time director of surgery on the Tuberculosis Service of Bellevue Hospital. Col. Berry was also of great assistance, subsequently, in putting the plan into effect.

The investigation was made practicable through the action of the Bellevue Hospital Medical Board, making available all of the admission facilities of the Hospital.

In carrying out the research work itself, three groups of investigators have collaborated: one group under Richards and Cournand of the department of medicine, College of Physicians and Surgeons, responsible for general hemodynamics and respiratory studies; a group under Gregersen of the department of physiology, College of Physicians and Surgeons, responsible for blood volume studies; and a group under Dr. Smith, of the department of physiology, New York University College of Medicine, responsible for arterial pressure recording, and for studies of renal function.

PROCEDURE

Each patient was seen as soon as possible after admission by a member of the research group, and a consultation held with the surgeon in charge. An evaluation of the clinical signs and symptoms was made, and if the case was considered suitable, the investigative studies were then started immediately. An attempt was made to obtain the first series of measurements before any treatment had been instituted.

The patient was weighed by suspending him from a hanging scale by means of ropes attached to the four corners of a canvas stretcher. His height was determined with a measuring tape. To facilitate fluoroscopy, he was placed on a special fracture bed of which the mattress and springs were replaced by tightly drawn canvas straps. Catheterization of the right auricle of the heart, under fluoroscopic control, was then performed; the catheter's position was further established by anteroposterior and lateral x-rays. While this was being done, a 19 gauge Ungar needle, with tight-fitting obturator,* was introduced into a femoral artery and another into a peripheral vein, and left in place throughout the series of measurements. Both auricular catheter and venous needle were kept patent by a slow continuous flow of saline solution. The determination of blood volume was begun. Simultaneous readings of auricular pressure and peripheral venous pressure were taken, and intra-arterial pulse tracings were recorded optically from the femoral artery, by Hamilton's method. Samples of blood and expired air, for cardiac output determination by the direct Fick method, were then taken, followed by another arterial pressure tracing and (in earlier cases) by a ballistocardiographic tracing. Finally, glomerular filtration and plasma flow through the kidneys were studied by clearance techniques.

*Specially designed and provided through the courtesy of Becton, Dickinson and Co.

Clinical signs and symptoms and any changes in the patient's condition were noted in the protocol. All medication and fluids were also noted, and the amount of blood withdrawn was recorded, and that otherwise lost was estimated when possible. Roentgenograms were taken to record the position of the catheter in the heart.

The whole series of studies was repeated at intervals before and after therapy when this could be done without interfering with the clinical management of the case.

METHODS

Plasma Volume, Serum Protein, and Hematocrit.—Determinations of the plasma volume were made with the T-1824 method (Gregersen and co-workers[1]). Depending upon the weight of the patient, 4 or 5 c.c. of 0.4 per cent dye were injected into the peripheral venous needle with a calibrated 5 c.c. syringe. If repeated withdrawal of venous blood for the purpose of rinsing the syringe became difficult, rinsing was done with saline solution from a reservoir connected to the needle with a watertight three-way stopcock. The dye-free control sample and subsequent dye-tinged samples (collected at 5-minute intervals during the first half hour, and then at 10-minute intervals) were drawn from the arterial needle. The blood was placed in oiled tubes and the concentration of dye (expressed as optical density) in each serum sample was determined with a Koenig-Martens visual spectrophotometer (Gregersen[2]). The plasma volume was calculated from the equation:

$$\text{Plasma volume in c.c.} = \frac{\text{c.c. dye injected} \times 250 \times K}{C_o}$$

in which K is the optical density of the dye solution diluted 1:250 in serum, and C_o is the initial dye concentration (expressed as optical density) derived by extrapolation of the dye curve on a semilog plot (Gregersen and Rawson, in press). As described elsewhere, the effects of fluid shifts on the dye curve were always considered in the final analysis of the data (Gregersen and Noble, to be published).

The serum protein values reported in the tables of results were determined with the falling drop method (Barbour and Hamilton[3]), the formula of Weech, Reeves, and Goettsch[4] being used for conversion of serum specific gravity to serum protein content. Hematocrit values were obtained on arterial samples using 1 c.c. Wintrobe tubes and crystalline heparin as anticoagulant, after 40 minutes' centrifugation at 2,500 r.p.m.

The total blood volume was calculated from the plasma volume and the arterial hematocrit according to the formula:

$$\text{Total blood volume in c.c.} = \frac{\text{plasma volume in c.c.}}{100 - \text{hematocrit \%}} \times 100$$

The value so obtained is higher than the true blood volume because

the per cent cells obtained by centrifugation includes a small amount of plasma trapped in the cell mass (Gregersen and Schiro) and because the per cent erythrocytes in the blood from large vessels is higher than the body hematocrit.[5-8] Nevertheless, the calculation is appropriate for the present purpose since we are comparing the results with average normal values derived in the same manner. Discussion of this question will be found in a separate paper which deals with the mixing time and disappearance rate of T-1824 in human cases of shock, and with the evidence that this dye measures the plasma volume in shock. It may be stated here, however, that evidence of increased capillary leakage was not found in cases of shock from skeletal trauma or hemorrhage. The dye disappearance rates were approximately the same during shock as after recovery.

Catheterization of the Right Heart. Auricular and Venous Pressures.—The catheterization of the right auricle was carried out by cutting down on a median basilic vein of either right or left arm, and running in a No. 8 or No. 9 ureteral catheter,* according to the technique of Cournand and associates.[9] Continued experience with this procedure has proved its safety, no unfavorable complications having arisen in over 150 catheterizations, beyond occasional linear mural thrombosis near the site of the incision. The catheter has been left in place continuously for as long as twenty-four hours. It was frequently most useful as a means of administering blood or other fluids.

Auricular pressure readings were taken by the use of a saline manometer,[10] and peripheral venous pressures recorded in the same manner, on a second manometer. The levels of venous and auricular pressures were recorded, using as the zero point the position of the tip of the catheter in the right auricle (established by lateral x-ray).[10]

The average vertical distance in thirty cases, from the angle of Louis on the external surface of the chest to the tip of the catheter in the right auricle, was 66 mm., S.D. ± 13.

The true criterion of adequacy of return of venous blood to the right heart is the "effective pressure" in the right auricle; that is, the mean right auricular pressure relative to the atmospheric pressure, plus the amount of the mean negative intrathoracic pressure as it exists in the region of the right auricle. There are two respects in which the auricular pressure, as measured by our technique, deviates from this ideal value.

One hydrostatic element that may be somewhat variable is the depth of the chamber constituting the right auricle. The catheter, according to x-ray evidence, lies almost always along the dorsal wall of the auricle. A deep right auricle would give a somewhat higher level of pressure, as recorded on the manometer, than a shallow one. It is possible that

*Specially designed and provided through the courtesy of the United States Catheter and Instrument Corp., Glens Falls, N. Y.

a poor venous return might result in some flattening of the antero-posterior diameter of the auricle, with the patient lying supine. As a source of error of mean auricular pressure, however, this factor is probably not large.

More important is the pleural pressure. Abnormal breathing may produce changes in either direction. With hyperventilation, however, the pleural pressure usually becomes more negative, especially if the breathing is asthmatic or stertorous. This means that the effective pressure at the right auricle will be larger, for the same (atmospheric) level of the right auricular pressure. A further source of error is that with this type of breathing, the auricular pressure as recorded is usually nearer the inspiratory level, since saline solution is sucked out of the long catheter more readily than blood is forced back in.[10] If the breathing is unimpeded, however, and relatively quiet, it is probable that auricular pressure levels can be compared with normal values, and that changes occurring in the clinical course of the individual case will represent corresponding changes in effective venous return.

Arterial Blood Pressure.—Arterial pressure was measured in the femoral artery by a Hamilton optical manometer,[11] mean pressure being determined by planimetric integration of the area under the pressure pulse curve.

Cardiac Output by the "Direct Fick" Method.—The direct Fick determination[9] of cardiac output requires simultaneous sampling of mixed venous blood, arterial blood, and expired air.

After flushing out the saline solution in the catheter by withdrawing 5 to 10 c.c. of blood back through it, a 15 c.c. sample of mixed venous blood was then taken under 5 c.c. of oil in a syringe. Air contamination was excluded by a tight rubber adapter and a Luer-lock connection. Arterial blood was similarly collected in an oil syringe attached directly to the indwelling arterial needle. Both samples were immediately transferred to iced blood bottles containing 10 c.c. of oil, previously boiled to remove the air, and crystals of anticoagulant (0.6 mg. sodium fluoride and 4.5 mg. neutral potassium oxalate dried in autoclave). They were stirred slowly to prevent settling of red blood cells, taken directly to the laboratory, and analyzed immediately for oxygen and carbon dioxide.

Expired air was collected and measured in a Tissot spirometer or Douglas bag. A rubber mouthpiece and noseclip were usually found satisfactory, but it was frequently found necessary to hold the patient's lips tightly around the mouthpiece. Occasionally in an unconscious patient who required a metal pharyngeal airway, an anesthesia mask was used and care taken to avoid leaks. The spirometer or Douglas bag had been flushed out with expired air a few minutes before the expired air sample was taken for analysis.

Expired air was collected over an accurately measured interval, from 1 to 2 minutes. Fifteen seconds after the start of the expired air col-

lection, mixed venous blood sampling was begun, followed 15 seconds later by arterial blood sampling. Each blood sample required about 25 seconds to collect and so was spread out over a considerable part of the air-sampling period. The pulse was counted throughout the sampling procedures.

Carbon dioxide and oxygen contents of mixed venous and arterial blood were done in duplicate on the Van Slyke-Neill apparatus. Expired air samples were analyzed in the Haldane apparatus to determine oxygen intake and carbon dioxide output per minute.

According to the Fick equation:

$$\text{Cardiac output (l./min.)} = \frac{O_2 \text{ intake (c.c./min.)}}{O_2 \text{ arteriovenous diff. (c.c./l. blood)}}$$

or

$$\text{Cardiac output (l./min.)} = \frac{CO_2 \text{ output (c.c./min.)}}{CO_2 \text{ arteriovenous diff. (c.c./l. blood)}}$$

Cardiac output was calculated independently from the carbon dioxide and from the oxygen data, and the average value taken. Cardiac index in l. per min. per square millimeter body surface and stroke volume in cubic centimeters per beat were also calculated.

A brief comment upon the validity of this method follows:

TABLE I

VALUES OF OXYGEN AND CARBON DIOXIDE IN SUCCESSIVE SAMPLES OF MIXED VENOUS (RIGHT AURICLE) BLOOD

PATIENT	CO_2 CONTENT, VOL. PER CENT		O_2 CONTENT, VOL. PER CENT	
	(1)	(2)	(1)	(2)
F. C.	56.2	55.4	11.2	11.2
G. B.	54.1	53.9	3.9	4.1
T.	54.5	55.4	5.9	6.3
D.	54.0	55.6	6.8	7.3
F. K.	57.2	57.4	12.4	12.9
W. D.	52.5	52.8	--	--
M. W.	--	--	12.0	11.8
Y. C.	54.4	54.9	12.8	13.0
O. K.	50.6	50.2	10.5	10.0
T. C.	47.6	47.4	10.6	10.4
V.	57.0	53.8	13.6	14.1
D. J.	41.6	42.7	11.3	11.3

Mixed venous blood sample: The most important question is whether the sample of blood taken from the right auricle can be relied upon to represent true mixed venous blood. The best evidences that we have at present on this point are: (1) A series of eleven patients, from each of whom repeated samples were taken within a few minutes' time, with the subject in an apparently steady state (Table I). It will be seen that values of mixed venous oxygen remained fairly steady; there were no differences between successive samples larger than 0.5 volume per cent. The agreement in the CO_2 values was not as good. (2) A series of ten patients (all but one being normal subjects, or subjects with

arterial hypertension), from each of whom samples from the right ventricle and right auricle were drawn within a few minutes' time. The average difference in O_2 content between the two samples was .11 vol. per cent, the largest difference being .3 vol. per cent. The carbon dioxide contents were not as constant, the average difference being .63 vol. per cent, the largest 2.1 vol. per cent. In four cases of this series a second auricular sample was taken immediately after the first, after the tip of the catheter had been withdrawn further into the auricle, nearer to the superior vena cava; in two instances the O_2 content of both auricular samples checked within .1 vol. per cent; in the other two a rather large discrepancy was noted, amounting to .9 and 1.1 vol. per cent respectively. Although these observations are still too few, they suggest that in normal subjects the oxygen content of the auricular blood is the true "mixed venous" oxygen, providing that the tip of the auricular catheter is accurately located close to the tricuspid valve.

TABLE II

COMPARISON OF CARDIAC OUTPUT CALCULATED BY THE DIRECT FICK METHOD AND BY THE BALLISTOCARDIOGRAM

PATIENT	CONDITION	TOTAL BLOOD VOLUME (C.C. PER SQ. M. B. S.*)	HEMATOCRIT (%)	CARDIAC OUTPUT		
				FICK (L. PER MIN. PER SQ. M. B. S.)	BCG. (L. PER MIN. PER SQ. M. B. S.)	DIFFERENCE $\frac{CO_F - CO_B}{CO_F} \times 100$
J. H.	Head injury, coma	2850	43	3.02	2.69	+10.8
J. L.	Skeletal trauma, no shock	2260	41	3.08	3.12	−1.4
S. V.	Skeletal trauma, no shock	3860	43	4.15	3.77	+9.2
A. V. H.	Recovery from burns	2760	37	3.91	3.49	+10.7
J. E.	Recovery from hemorrhage	3310	37	4.45	4.34	+1.8
E. C.	Recovery from hemorrhage	3110	25	3.24	2.45	+24.5
J. E.	Severe hemorrhage	2070	38	2.99	5.04	−55.6
E. C.	Severe hemorrhage	2290	24	2.45	3.30	−40.5
E. C.	Further bleeding	2120	18	2.46	4.28	−71.5
McN.	Skeletal trauma, mild shock	1900	25	2.56	3.10	−20.8
M. C.	Skeletal trauma, milk shock	2495	34	2.18	3.79	−73.9
Y. T.	Burns, mild shock	2272	58	1.62	1.70	−4.9

*Cubic centimeter per square meter of body surface.

Arterial blood: This is a reliable sample. The arterial needle remains in place throughout the series of measurements, and there is thus no pain at the time the arterial blood sample is taken.

Expired air: It may well be argued that a 1-minute sample is too short and it is true that there may be some error due to this. Patients in shock, however, are often restless and a longer period of collection of expired air may result in struggling or other effort which produces a still greater error.

The figures for cardiac output in this report have been calculated as the mean of the two separate values determined from the carbon dioxide in blood and expired air, and from the oxygen respectively. The chief reason for this has been that the use of two values provides a certain internal check on the validity of technique. Later work may show, as the comparisons just given suggest, that it will be more accurate to use

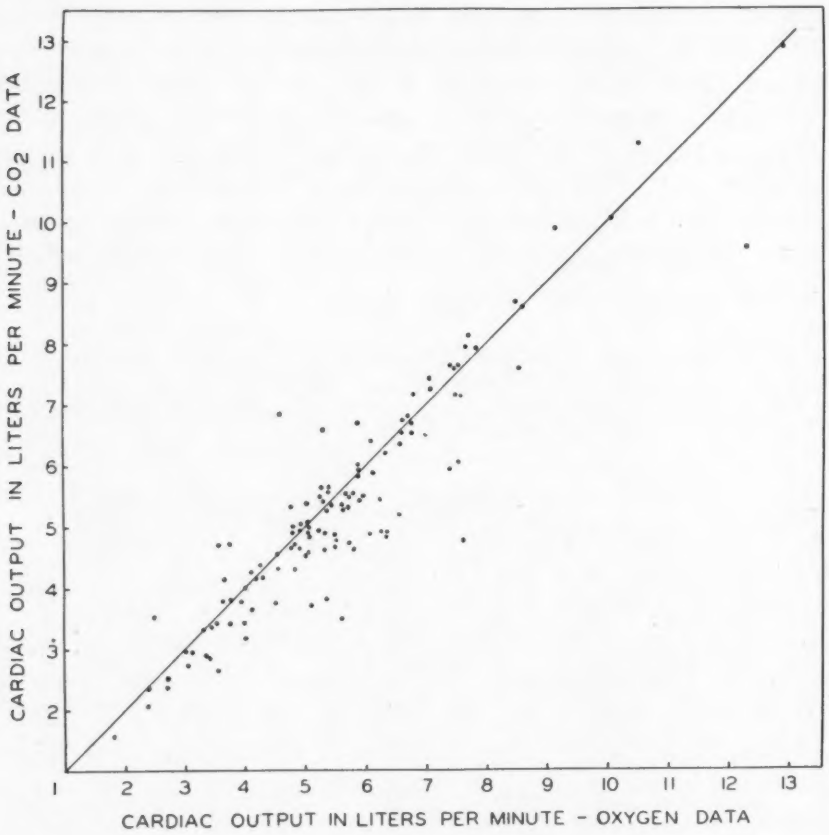

Fig. 1.—Scatter diagram showing the correlation between cardiac output calculated from CO_2 data and cardiac output calculated from O_2 data in 120 cardiac output determinations by the direct Fick method. The straight line is the line of identity. Although the mean of the values based on oxygen data is slightly higher than the mean of those based on CO_2 data, this difference is not significant.

only the oxygen transport figures. No significant differences should occur, however, in groups of data, on this account. In Fig. 1 are plotted cardiac output figures in 118 determinations, including 59 determinations made on the patients reported in the present paper, ordinates indicating the value by CO_2, and abscissas by O_2 calculation. There is a good correlation. The mean cardiac output by CO_2 is 5.24 liters per minute; 5.51 liters per minute by O_2. The difference of means equals 0.27; standard error of difference of means equals 0.23. This difference between O_2 cardiac output and CO_2 cardiac output is statistically not significant. Cardiac output figures calculated sepa-

rately from the CO_2 and the O_2 data, in patients in shock, provide a better correlation than in normal subjects.

Control values of cardiac output and related measurements in fifteen normal subjects, studied under similar conditions, appear in Tables III and IV. The average values for cardiac index, stroke volume, and arteriovenous oxygen difference were respectively 3.42 liters per minute per square meter of body surface, 83 c.c. per beat, and 45 c.c. per liter of blood. The values for cardiac output and stroke volume are higher and figures for arterovenous oxygen difference are lower, than corresponding figures reported on the basis of foreign gas methods. It will be noted that the O_2 consumption per square meter of body surface in this series of fifteen normal individuals was somewhat high, indicating that some subjects at least were not in basal metabolic condition at the time of study. There are, however, reasons to believe that accepted figures for cardiac output as given by foreign gas methods are too low; a more complete discussion of this question will be published elsewhere.

Cardiac Output by the Use of the Ballistocardiogram.—During the early part of the investigation, ballistocardiographic tracings were taken as nearly as possible to the time of the cardiac output determination by the direct Fick method. The procedure followed was comparable to that previously described in normal individuals.[9] It soon became evident that in many instances the ballistocardiographic tracings were greatly influenced by the increased respiratory effort that was encountered. In Table II the results of twelve double determinations in nine subjects are listed, in which this disturbing factor was minimal. It can be seen that a reasonable agreement existed in subjects not in shock and with relatively large cardiac outputs. The cardiac output by the direct Fick method tended to be somewhat larger than the cardiac output calculated from the ballistocardiogram, even after the correction for cross section of the aorta had been introduced.[9] On the other hand, in patients suffering from shock, with one exception (Y. T.), differences were very significant and all in the other direction; that is, the data calculated from the ballistocardiogram were consistently larger. The data on two subjects, J. E. and E. C., repeatedly studied while in a state of shock following severe gastric hemorrhage, and again after recovery, emphasize strikingly the fair agreement in the latter state, and the large discrepancy in the former. Apparently some fundamental change occurs in the state of shock which invalidates assumptions upon which Starr's formulas were based. The two following suggestions are made: that as a result of marked decrease in blood volume, the capacity of the aorta and thereby its cross section is reduced; that the ejection velocity is increased as compared to that in normal conditions, an assumption supported by the change in contour (sharp initial peak) for the pressure curves in conditions with di-

TABLE III

HEMODYNAMICS AND BLOOD VOLUMES

TYPE OF INJURY	NO. CASES	PULSE RATE	ARTERIAL PRESSURE			VENOUS PRESSURE (MM. H_2O)	AURICULAR PRESSURE (MM. H_2O)	CARDIAC OUTPUT		O_2 A-V DIFFERENCE (C.C. PER L. BLOOD)	PERIPHERAL RESISTANCE (DYNES CM.$^{-5}$ SEC.)	BLOOD VOLUMES		HEMATOCRIT (% R.B.C.)	SERUM PROTEINS (GM. %)
			SYST. (MM. HG)	DIAST. (MM. HG)	MEAN (MM. HG)			CARDIAC INDEX (L. PER MIN. PER SQ. M.)	STROKE VOLUME (C.C. PER BEAT)			PLASMA (C.C. PER SQ. M.)	WHOLE BLOOD (C.C. PER SQ. M.)		
Normal Cases	15														
High		96	149	83	106	--	--	4.25	109	60	1755	--	--	--	--
Low		51	122	68	88	--	--	2.12	63	35	1100	--	2670	40	--
Average		74	137	74	97	74	33	3.42	83	45	1290	1600	2900	45	7.00
Skeletal Trauma															
No shock	8														
High		98	167	87	113	92	70	4.32	100	50	1635	2070	3300	48	7.05
Low		70	102	44	67	79	12	2.24	52	40	952	1130	1910	35	5.66
Average		80	137	69	94	86	45	3.57	78	46	1281	1597	2791	41	6.35
Mild shock	4														
High		140	113	50	67	105	47	2.71	39	82	1452	1675	2500	43	5.49
Low		100	48	28	36	62	10	2.18	33	58	738	1376	1900	25	4.76
Average		120	77	40	54	77	26	2.46	36	71	1019	1532	2330	34	5.22
Moderately severe shock	4														
High		205	80	42	57	121	0	3.01	35	100	1468	1310	1820	37	5.91
Low		112	46	15	22	50	-11	1.30	21	60	567	1033	1540	28	5.17
Average		137	63	32	44	90	-8	2.06	26	84	1021	1125	1670	32	5.54

Hemorrhage	4													
High		131	135	95	105	48	24	2.99	44	84	2200	1730	2120	40	6.68
Low		96	49	24	32	29	−31	1.38	17	57	828	850	1410	18	4.45
Average		113	94	54	64	41	−1	2.20	31	70	1542	1325	1908	32	5.63
Burns*	4													
High		112	136	71	100	--	42	2.30	78	106	3186	1230	2750	58	6.54
Low		58	53	28	38	--	14	1.05	14	54	678	960	2120	42	6.23
Average		91	--	--	--	--	--	1.81†	39	--	--	1100	2320	51	6.44
Abdominal Injuries														
No shock	3													
High		128	182	94	132	85	31	4.48	85	64	2223	1700	3470	52	6.19
Low		80	103	54	70	45	25	2.92	53	35	757	1075	2110	49	4.97
Average		99	130	72	91	61	27	3.77	66	50	1260	1490	2993	50	5.74
Shock	3													
High		156	112	48	69	39	3	3.24	38	97	1420	1360	2600	54	7.04
Low		76	40	20	28	--	−30	1.24	22	73	640	--	--	44	5.60
Average		111	78	33	48	--	−8	2.27	33	88	1133	--	--	49	6.38
Head Injuries	6													
High		104	186	100	135	99	44	4.46	86	96	1710	1790	3070	45	7.29
Low		57	131	74	96	35	−36	2.62	72	29	1122	1210	2590	39	5.75
Average		79	157	85	111	65	6	3.66	79	62	1476	1563	2865	43	6.85

*In two cases, measurements were incomplete; average was calculated only if measurements were complete in all four cases.
†In one case, cardiac output figures from ballistocardiogram.

TABLE IV

VENTILATION, RESPIRATORY GAS EXCHANGE, AND RESPIRATORY GASES IN BLOOD

TYPE OF INJURY	NO. CASES	RESPIRATION RATE	VENTILATION (L. PER MIN. PER SQ. M.)	GAS EXCHANGE		ARTERIAL BLOOD							MIXED VENOUS BLOOD		
				O_2 INTAKE (C.C. PER MIN. PER SQ. M.)	RESP. QUOT.	CO_2 (VOL. %)	pCO_2 (M.M. HG)	T_{40} (CO_2 VOL. % AT 40 MM.)	pH_s	O_2 CONT. (VOL. %)	O_2 SAT. (%)	HB. (GM. %)	pCO_2 (M.M. HG)	pH_s	O_2 SAT. (%)
Normal Controls	15														
High		30	6.62	186	1.02										
Low		12	2.95	118	.61										
Average		18	5.07	154	.84	49.1	38.8	49.5	7.42	16.6	96.0	13.0	44.7	7.39	67.7
Skeletal Trauma															
No shock	8														
High		22	6.28	213	.86	50.6	42.8	49.0	7.43	18.5	97.4	14.2	48.2	7.39	76.3
Low		17	4.36	151	.66	42.7	30.4	41.8	7.36	13.1	91.0	10.7	38.3	7.33	58.0
Average		18	5.21	184	.74	44.1	37.4	45.0	7.39	15.6	94.2	12.3	43.9	7.36	66.7
Mild shock	4														
High		34	9.62	189	.80	40.1	33.4	44.0	7.41	14.4	95.0	12.5	39.5	7.35	42.9
Low		22	5.77	160	.65	32.7	27.0	37.0	7.32	9.8	85.7	8.0	32.0	7.29	35.0
Average			7.73	174	.70	35.8	30.5	40.2	7.38	12.3	90.8	10.1	36.9	7.32	38.4
Moderately severe shock	4														
High		36	18.46	285	.99	39.4	39.4	39.8	7.29	14.6	99.0	11.0	46.7	7.26	49.6
Low		17	4.35	131	.83	16.5	17.4	25.5	7.26	10.2	83.0	8.0	31.4	7.19	14.0
Average		29	11.19	176	.89	28.0	28.4	32.7	7.28	11.8	94.6	9.3	40.9	7.22	28.2

Hemorrhage	4													
High		24	9.95	223	.75	57.2	53.6	53.4	7.37	14.6	97.1	11.6	66.0	7.33	48.0
Low		16	4.53	119	.70	30.3	25.7	36.4	7.30	6.6	95.2	5.1	32.2	7.28	16.2
Average		21	6.35	154	.73	38.2	34.6	40.9	7.34	11.5	95.9	9.1	42.6	7.32	36.4
Burns*	4													
High		22	4.10	126	.82	40.2	41.9	45.4	7.46	19.4	95.1	15.3	47.2	7.43	68.6
Low		8	2.41	109	.68	36.7	30.8	39.3	7.29	15.7	87.0	12.3	35.8	7.23	42.3
Average		14	3.15	117	.74			41.8		18.0		14.5			
Abdominal Injuries														
No shock	3													
High		32	9.41	193	.75	50.8	46.5	48.0	7.42	20.0	95.7	15.6	37.5	7.39	74.0
Low		21	5.81	154	.72	28.6	27.7	33.9	7.32	17.2	93.0	13.8	32.0	7.29	62.0
Average		27	7.43	178	.73	37.8	34.2	40.7	7.38	18.4	94.5	14.6			69.0
Shock	3													
High		45	12.30	236	.87	33.0	41.7	39.6	7.43	21.2	94.8	17.2	51.8	7.40	60.2
Low		40	9.26	129	.73	29.0	26.3	28.4	7.17	12.0	72.8	12.3	32.7	7.12	15.2
Average		42	10.63	189	.78	31.2	33.6	34.4	7.31	17.1	86.5	14.6	43.0	7.27	40.0
Head Injuries	6													
High		38	14.32	353	.84	47.7	40.7	48.0	7.55	26.8	96.2	22.5	46.4	7.49	79.2
Low		12	4.99	155	.69	37.7	24.8	44.9	7.38	15.4	88.8	11.9	29.2	7.34	34.3
Average		23	10.00	247	.75	42.3	32.5	46.1	7.46	18.1	91.5	14.6	38.3	7.42	62.6

*See note Table III.

minished filling of the arterial system (Wiggers). In either case the ballistocardiograph as calculated would give too high values.

As a result of these studies, we were led to discard the ballistocardiogram for the study of variations of circulation in patients in or recovering from shock.

Peripheral Resistance.—The total peripheral vascular resistance, R, was calculated from the formula:

$$R = \frac{Pm \text{ (mean pressure in mm. Hg)} \times 1332}{C.O. \text{ (cardiac output in c.c. per sec.)}}$$

The total peripheral vascular resistance, expressed in $\frac{\text{dynes sec.}}{\text{cm}^5}$ represents the total fall of pressure from the root of the aorta to the right auricle per unit of total blood flow per second.[12] Mean pressure in the femoral artery is assumed to be equal to mean pressure in the aorta, and since auricular pressure, expressed in mm. Hg, is virtually zero, it is neglected.

The total peripheral resistance is an overall measurement of resistance to flow and, as such, does not permit differentiation of local vascular changes and compensations. Local variations in resistance to flow are mostly contributed to by cross-sectional changes in vessels; however, changes in viscosity, especially at low pressure, are not a negligible factor.

As for interpretation, it can be tentatively stated that: (1) A calculated resistance within normal range does not exclude vasoconstriction in some areas if compensated by decreased resistance to flow in other areas. (2) A calculated resistance greater than normal may indicate (a) a predominance of vasoconstriction in some areas over vasodilatation or normal vascular tone in other areas; (b) an increase in viscosity; (c) a combination of both. (3) A calculated resistance lower than normal may result from (a) predominance of vasodilatation in some areas over vasoconstriction in others; (b) a decrease in viscosity; (c) a combination of both.

Respiratory Gases in Blood.—The following information was obtained for both mixed venous and arterial blood:

CO_2 content of blood, vol. %	$(CO_2)^b$
CO_2 content of serum, vol. %	$(CO_2)^s$
CO_2 tension, mm. Hg	pCO_2
CO_2 content at 40 mm. tension (alkali reserve), vol. %	T_{40}
Hydrogen-ion concentration at 37° C.	pHs
O_2 content, vol. %	
O_2 capacity, vol. %	HbO_2
O_2 saturation, %	%

CO_2 content, O_2 content, and O_2 capacity were determined directly and O_2 saturation calculated. In 68 per cent of the cases, hydrogen-ion

concentration was determined by the glass electrode method. A modified form of the MacInnes and Belcher glass electrode was used. The design permitted its being filled with mercury so that blood could be transferred from a pipette without contact with air. Samples were analyzed within fifteen minutes of the time they were drawn. Frequent control determinations with buffer solutions of known pH were made between sample determinations. $(CO_2)^s$ and pCO_2 were calculated, using the line charts of Van Slyke and Sendroy. The CO_2 content at 40 mm. CO_2 tension was estimated by making use of the alignment chart of Henderson, Bock, Dill, and Edwards.[13]

In 32 per cent of the cases one or two points on the CO_2 dissociation curve were determined by the tonometer technique. Use was made of the Henderson, Bock, Dill, and Edwards chart in the calculation of pCO_2 and T_{40} and of the Van Slyke and Sendroy line charts in the determination of $(CO_2)^s$ and hydrogen-ion concentration. Normal control values appear in Table IV.

Lactic Acid.—Lactic acid was determined by oxidation with ceric sulfate according to the microdiffusion method described by Winnick.[14] A misleading statement made by Gordon and Quastel[15] concerning the absence of oxidation of ethyl alcohol by ceric sulfate, invalidated at first all determinations made in subjects studied in a state of alcoholism. More recently, a modification of the original method has been developed, making possible the accurate determination of lactic acid in the presence of alcohol. Other controlled experiments have indicated that the presence of mannitol, a substance used for the measure of plasma flow through the kidney, has no effect upon lactic acid determinations.

Renal Clearances.—The renal clearance of mannitol has been used as a measure of the glomerular filtration rate[16] and the clearance of p-aminohippurate as a measure of the renal plasma flow.[17] Priming doses of 18 Gm. of mannitol,* and of 16.8 mg. per pound of body weight of p-aminohippurate were given intravenously, followed by intravenous infusion of 5 per cent mannitol and 200 to 300 mg. per cent p-aminohippurate solution at a rate of 4 c.c. per minute. After a 15-minute discard period, urine was collected by indwelling catheter and arterial blood taken at intervals. Mannitol in cadmium filtrates of plasma and in diluted urine[18] was determined by the modification of the method of Silberstein, Rappaport, and Reifer,[19] described by Smith, Finkelstein, and Smith.[16] Sodium p-aminohippurate was determined in the same cadmium filtrates and urines by a colorimetric method.[20]

In addition to (a) glomerular filtration and (b) plasma flow expressed in cubic centimeters per minute, the following data were calculated: (c) Filtration fraction, the proportion of the plasma flowing through the kidney, which is filtered at the glomeruli; (d) effective

*The mannitol and p-aminohippurate, etc., used in this study were supplied by Sharp and Dohme.

renal blood flow, calculated from plasma flow and hematocrit by the formula

$$\text{R.B.F.} = \frac{\text{clearance of p-aminohippurate}}{100 - \text{hematocrit } \%} \times 100$$

(e) Renal fraction, the percentage of the total cardiac output which passes through the kidneys, expressed as

$$\text{R.F.} = \frac{\text{R.B.F., lit./min.}}{\text{C.O., lit./min.}} \times 100$$

The figure for cardiac output was taken either from the observation nearest to the time of renal study, if the patient's condition had not changed, or as an average of two cardiac output determinations, one before, the other after renal clearance studies, when the condition had changed. (f) Average urine flow in cubic centimeters per minute. This volume, as measured, has been influenced by the injection of hypertonic solution of mannitol, and thus is presumably greater than the true urine flow obtaining in the given state of the circulation at the time.

It is assumed that mannitol filtration is not altered during shock, and that the clearance of this substance is a measure of the glomerular filtration rate. In the case of sodium p-aminohippurate, however, it may very well be argued that anoxia in the course of shock causes decreased activity of the mechanism by which it is excreted into the tubules and thereby results in the failure of complete extraction. This would lead to falsely low values for the rate of renal plasma flow, and thus to falsely high values for filtration fraction. In the course of this investigation, the filtration fraction in the majority of instances so far studied has been either normal or quite low, in the presence of marked anoxia, and apparently a reduced effective renal flow.

MATERIAL FOR STUDY

The material upon which the present paper is based includes 36 cases, of which the patients in 16 were suffering from skeletal trauma, 4 from hemorrhage, 4 from burns, 6 from abdominal injury, and 6 from head injury.

Patients in the 16 cases of skeletal trauma all suffered from multiple, usually compound or comminuted, fractures of the limbs. Three among them had special features: one had fractured ribs with hemopneumothorax and paradoxical motion of the chest wall; another had, in addition to a fracture of the pelvis, a fractured skull and slightly bloody spinal fluid; a third developed a very severe infusion reaction during the course of the study. The patients in 8 out of these 16 cases were considered to be suffering from shock, when first observed. Repeat measurements were made after spontaneous clinical improvement or after institution of treatment of the shock condition.

The 4 cases of hemorrhage consisted of 2 subjects with massive hematemesis due to ulcer, one with intestinal bleeding due to a ruptured vein in the small intestine, and one with external bleeding from self-inflicted cuts of the neck and arms. All 4 patients were considered to be in shock of varying intensity at some time during the period of observation. One of these was found upon recovery to present evidence of arterial hypertension.

Four patients with burns were studied; in 2 of them approximately one-third of the body surface was involved; in 1, about one-quarter; and in the fourth, the face and both hands. Depth of burns ranged from first to third degree.

Three patients with abdominal injuries, suffering respectively from a ruptured peptic ulcer, a ruptured urinary bladder, and necrosis of the sigmoid and rectum following an enema with a caustic substance, were not considered to be in shock at the time of study. One of these cases, on recovery, was found to have arterial hypertension. The 3 other patients with abdominal injuries presenting clinical manifestations of shock, suffered from incarcerated hernia, ruptured ileum, and intestinal obstruction respectively. The patient with intestinal obstruction was in a moribund condition when studied.

The 6 cases of head injury were all comatose, and prognosis when first seen was considered to be fatal. At autopsy in addition to subdural and/or subarachnoid hemorrhage, multiple punctate hemorrhages of the pons and other parts of the brain stem were found. They were all first studied during the period of arterial hypertension and progressive hyperthermia, and then followed until death.

Sixteen, or 45 per cent of the total number of 36 patients died, and 11 were autopsied.

CLASSIFICATION AND CLINICAL MANIFESTATIONS

Primary subdivision of all clinical material on the basis of type of injury, as already indicated above, has been retained in the presentation of physiologic data, since the actual results were found to group themselves most satisfactorily in this manner.

A secondary differentiation as to the degree of shock has also been made. This has been done in the light of all available data, including the extent and time of injury, clinical manifestations on admission, the laboratory findings, and the subsequent clinical course.

Skeletal Trauma.—Of the 16 cases in this group, 8 were classified as having "no shock," 4 "mild shock," and 4 "severe shock."

In spite of the absence of specific clinical criteria by which to evaluate the severity of shock, the overall clinical impressions at the time of study of these 16 patients with skeletal trauma were fairly consistent with the classification made in retrospect. Thus, clinically, none of the patients in the "no shock" group were considered to be in shock

at the time of study, although, in most cases, shock had been anticipated because of the severity of the injuries. Of the 4 patients in the "mild shock" group, 1 showed no clinical evidence of shock and 2 appeared to be in moderately severe shock. One of the latter cases was complicated by chest injury, with paradoxical motion of the chest wall, and the other by acute alcoholism, both conditions having brought on shock-like symptoms which were difficult to evaluate. All 4 cases in the "severe shock" group were so described on clinical grounds.

More exact evaluation of the individual patient, on the basis of clinical manifestations, was most difficult, both because the signs and symptoms were so varied from one patient to another, and because such manifold changes frequently were seen in the same patient within a relatively brief period of time. A few general descriptive comments can be made.

Patients not in shock had more symptoms and fewer signs, those with severe shock fewer symptoms and more signs. Pain, for example, was present in all "no shock" cases, but absent in one-half of the cases with "mild" or "severe" shock. Apprehensiveness was less often seen in patients in severe shock in this group. These patients, in fact, were usually apathetic, quiet, cooperative, rational when roused, without physical complaint, and without anxiety. Not infrequently as a patient emerged from shock he began to be restless and complain of pain. They were usually much more disturbed about the various examinations made, after recovery, than they had been on admission, during shock.

Of individual symptoms, thirst was the most constant. Pallor and coolness of extremities paralleled in a general way the severity of shock; but the subjective sensation of cold might be complained of whether the patient was in shock or not. This sensation was often associated with some shivering. Transient nausea and vomiting occurred at some time in almost every case of shock. Sweating was frequent but usually a fleeting phenomenon. The arterial pulse in shock was thready, often imperceptible at the wrist; the rate was quite variable. The peripheral veins were usually small and collapsed; a needle could usually be introduced readily, though often blood could not be withdrawn. Cyanosis and mottling of the skin, usually a terminal finding, were occasionally seen in patients whose condition was not serious.

Hemorrhage.—The group of 4 hemorrhage cases was too small to subdivide. It is, therefore, not homogeneous either with respect to the type of bleeding or to the depth of shock. Some of the clinical manifestations, including thirst, mental and emotional depression, and thready pulse, corresponded closely to those of the skeletal trauma group. Pallor, coolness of the extremities, and collapsed veins were more prominent, while pain and sweating were less in evidence. The tendency to vomit could not be compared because of hematemesis in two of the cases.

Restlessness was observed in association with active bleeding at a time when the patient had already lost large quantities of blood.

Burns.—The patients in 3 out of 4 cases were considered to be in shock when first examined. In contrast to the previous group in shock, restlessness and pain were prominent; thirst and vomiting were also present.

Abdominal Injuries.—The differentiation of the cases of abdominal injury into those with and those without shock present was clear-cut, upon review of all the data. The 3 patients without shock were in good condition; all were operated upon successfully and recovered. The 3 others were in advanced shock: 1 died within an hour after the study was completed, the other 2 both died within twenty-four hours of the time of study.

In general, the patients with abdominal pathology showed more of the usual clinical signs and symptoms of shock than those with skeletal trauma or hemorrhage with a comparable degree of circulatory failure.

Head Injuries.—The head injury cases contrasted sharply with the other groups. Studied initially in the phase of hypertension and hyperthermia, they had bounding pulses and burning hot skin over the head and trunk. The extremities remained cool and dry. The respirations were both deep and rapid and frequently became stertorous due to falling back of the tongue or to partial obstruction of the airway by aspirated material. All patients in this group were comatose, had no cough reflexes, and vomited, making aspiration of vomitus into the lungs almost inevitable unless the stomach was kept empty by means of a Levine tube. A metal pharyngeal airway and frequent use of suction helped to maintain a free air passage. These patients showed none of the clinical manifestations of shock.

RESULTS

State of the Circulation in Various Types of Injury

In Tables III and IV and Fig. 2 are given, for each type of injury, the means and the range of variation of the following measurements: (a) Blood volume and its components, (b) arterial blood pressure, (c) right auricular and peripheral (arm) venous pressures, (d) cardiac output and the state of respiratory gases in arterial and mixed venous blood, and (e) respiratory gas exchange.

Inasmuch as the comparison sought for in the tabulation was the *state of shock* versus the *state of nonshock,* that particular series of measurements was chosen, on each patient in shock, which showed the greatest deviations from normal, i.e., the severest shock picture. The table contrasts the group picture, so to speak, of the circulation in shock, constructed in this way, against the group picture of the circulation of injured subjects not in shock. The progressive change, as a given patient moves from shock to recovery, is considered in a subsequent section.

For purposes of reference, at the top of the tables are given a set of normal values of the various functions measured.

Skeletal Trauma Without Manifestation of Shock.—The findings in this group may be compared to average values obtained in normal sub-

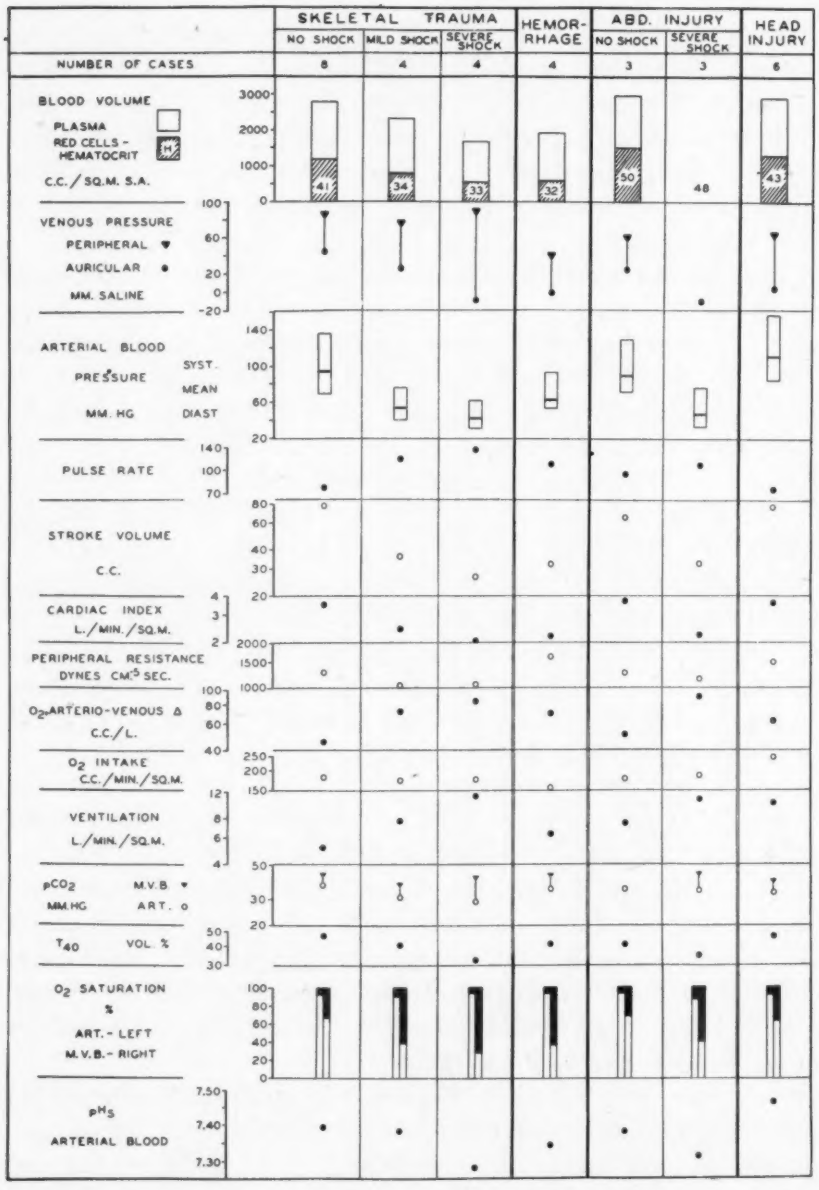

Fig. 2.—Graphic representation of average measurements shown in Tables III and IV. (For mode of grouping and description of measurements see text.)

Blood volume, venous and auricular pressures, arterial blood pressure, pH and O_2 saturation of arterial blood, measured by rectangular coordinates. All remaining measurements plotted against logarithmic ordinates. In the column of O_2 saturation, the solid block represents the O_2 unsaturation per cent, the open block the oxyhemoglobin per cent of total hemoglobin.

For approximate normal control values, see Tables III and IV. No values are plotted for blood volume and peripheral venous pressure in the abdominal injury group with severe shock, since the data for this group were incomplete.

jects. The metabolic conditions under which the two groups were studied, while not strictly basal in either group, were comparable.

It can be seen that the hemodynamic status of cases with severe trauma without clinical manifestations of shock, is close to normal. Differences in pulse rate, arterial, venous, and auricular pressures, blood volume, cardiac output, peripheral resistance, ventilation, oxygen consumption, and the oxygen saturation, carbon dioxide pressure, alkali reserve, and hydrogen-ion concentration of both arterial and mixed venous blood, are well within the range of normal variation. Hematocrit and plasma protein were slightly below normal figures. Thus, the injured individuals who showed no clinical or other manifestations of shock were found to have a circulatory status within normal limits except for slightly low hematocrit and plasma protein.

Skeletal Trauma With Mild and Severe Shock.—The picture of peripheral circulatory failure in these cases was definite and consistent, as shown in the tables and figure. The chief findings in severe shock may be grouped as follows:

Blood volume: Blood volume was sharply decreased, the average value being little more than one-half normal. Red cells were decreased more than plasma, as indicated by low hematocrit reading. In no instance, in this group, was there any evidence of hemoconcentration.

Intravascular pressures: Arterial blood pressure was low, average mean pressure being just under 40 mm. There was a tendency for systolic pressure to fall more than diastolic, pulse pressure thus being also diminished.

Pressures in the right auricle, expressed in relation to atmospheric pressure, were consistently below normal. Every patient in severe shock had an auricular pressure of 0 or below. Pleural pressures not having been measured, the effective pressure of venous return to the right auricle was not determined.

Peripheral (arm) venous pressures, on the other hand, were not decreased, sometimes even elevated above normal in severe shock.

Cardiac output: This fundamental function was decreased, the mean value in severe shock being less than two-thirds normal. There was one exception (Table I), patient A. A., who was having a severe shaking chill at the time of study, with a temperature of 103° F., rising shortly after to 107° F.

Respiratory gas exchange: Pulmonary ventilation was increased in severe shock, though not in every case; it was probably associated with uncompensated acidosis. Oxygen consumption, on the other hand, was slightly subnormal. The single exception here was, again, the patient with the shaking chill and high temperature. Arterial blood was normally saturated with oxygen, except in a few instances with known pulmonary disease. Mixed venous oxygen was therefore decreased ap-

proximately in proportion to the decrease in cardiac output. This is well shown in the chart.

Acid-base equilibrium: Alkali reserve and arterial hydrogen-ion concentration were both sharply decreased, an uncompensated acidosis. In some instances the acidosis was very marked. High blood lactic acid figures indicated that fixed organic acids played a large part in producing this change. Mixed venous hydrogen-ion concentration fell even more than arterial in shock, the arteriovenous differences in hydrogen-ion concentration being thus increased.

It was at first thought that an acidosis of this kind was an essential feature of the shock picture in skeletal trauma. In more recent studies (subsequent to the series here reported) we have found that in early shock (within the first two or three hours), pH is still normal, even though the degree of shock may be severe; uncompensated acidosis develops in succeeding hours.

Perhaps the most striking feature of the results in the group of cases in mild shock is that they are in every respect consistent with the findings in severe shock. In other words, in every significant measurement the value in mild shock lies between the two extremes, on the one hand the normal figure, on the other that in severe shock.

Hemorrhage.—The blood loss in the 4 cases comprising this group could not be quantitatively estimated with any degree of accuracy. Blood volume studies, however, indicate not only different amounts of bleeding but also differences in the extent of hemodilution. On an average, blood volume was about two-thirds of normal and midway between values observed in the mild and in the severe shock groups with skeletal trauma. Average values of auricular pressure, cardiac output, stroke volume, mixed venous oxygen and arterial hydrogen-ion concentration also fell between similar values in the two latter groups. However, there were some differences worth noticing between the group with hemorrhage and the groups with severe trauma in shock: (1) The proportionally higher value of arterial blood pressure and peripheral resistance in the hemorrhage group, (2) the lower oxygen consumption, (3) the lower ventilation resulting in somewhat higher pCO_2 values in both arterial and mixed venous blood, (4) the lesser pulse rate increase. It must be noted that average values of arterial blood pressure and peripheral resistance are somewhat distorted by the values observed in one subject (E.C.) who later was proved to be suffering from arterial hypertension; nevertheless, one patient (C.F.) to be discussed in the second paper in greater detail, with the lowest blood volume and cardiac output of the group, still maintained a relatively high arterial blood pressure, and had therefore by calculation an abnormally high peripheral resistance.

In summary, apart from the differences noted above, which may be chance variations and which require further investigation, the status

of circulatory dynamics in patients with hemorrhage is closely similar to that in patients in shock due to severe trauma.

Burns.—This group is not very homogeneous with regard to extent of burns, or the time intervals between injury and study. The initial measurements were, however, taken before treatment with plasma had been started. In addition, because of technical difficulties due to the distribution of burns, some of the measurements are missing. Description of individual cases (to be reported later), followed over a long period of time, will give a more complete picture especially with regard to the relation of plasma loss to hemodynamic change. Certain definite trends, however, can be noted (Tables III and IV): (1) The large decrease in plasma volume with high hematocrit and relatively normal plasma protein; (2) the consistently low figures for cardiac index and stroke volume; (3) the lesser increase in pulse rate than in other groups; in one patient with severe shock, and very low blood pressure, the pulse rate was 58; (4) the low ventilation and low oxygen consumption; (5) the rather small decrease in alkali reserve.

Abdominal Injury Followed by Prompt Recovery.—This group of 3 patients was not in shock and the state of their circulation was normal. A further proof of their condition was that all three underwent major operative procedures shortly after study, and made uneventful recoveries.

With minor variations, values for blood volume, auricular and peripheral venous pressure, cardiac output, stroke volume, and arteriovenous difference were well within the normal range. Due to findings in one patient, who later proved to be hypertensive, the average arterial blood pressure was slightly above normal; the range of values of peripheral resistance on this account is quite large. Consistent with the normal state of circulation were the normal state of respiratory gases, alkali reserve, and level of hydrogen-ion concentration in both arterial and mixed venous blood. As expected with infradiaphragmatic pathology, resulting in distended and rigid abdominal wall, there was some hyperventilation. The single striking difference between this group and that represented by normal controls and by patients with skeletal trauma not in shock, was the high hematocrit. Infection, fever, vomiting, and the relatively long duration of some of these abdominal conditions may have been factors responsible here.

Abdominal Injury Followed by Death.—In this group of 3 patients, all in profound shock, death occurred within a short period of time following observation. In only 1 case was blood volume measured; this was only slightly below normal figures. Average figures of arterial blood and auricular pressure, of cardiac output and stroke volume were all low; in 1 patient, who died within one hour, the lowest figure of cardiac output of the series was recorded. Hyperventilation was marked, arterial hydrogen-ion concentration low, and the arteriovenous

difference in pCO_2 was large. Again in this group, hemoconcentration was present to the extent that hematocrit was high, although plasma protein concentration was normal.

Fatal Head Injury During Period of Arterial Hypertension.—The group of 6 cases with extensive brain damage was first studied during the period of arterial hypertension, which preceded death by variable but always brief intervals of time. The state of the circulation was then in sharp contrast with that observed in patients with severe skeletal trauma and shock, hemorrhage, burns, and fatal abdominal injury. With a blood volume on the low side of normal, the cardiac output was either normal or somewhat elevated. Wide variations in auricular pressure, resulting from very abnormal depth and quality of respiration, either gasping and stertorous as in most instances, or groaning, rendered any reading difficult to record and interpret. The peripheral resistance was on the upper side of normal. Apart from a tendency to gaseous alkalosis resulting from hyperventilation, all findings in arterial and mixed venous blood were normal.

Changes in Circulation Occurring During Recovery From Shock

Data in 6 subjects, 4 with skeletal trauma and 2 with hemorrhage, who were studied in the state of shock and again shortly after recovery from shock, following blood transfusion, are tabulated in Table V.

TABLE V

COMPARISON OF AVERAGE MEASUREMENTS IN STATE OF SHOCK AND AFTER RECOVERY FROM SHOCK, FOLLOWING BLOOD TRANSFUSION, IN SIX SUBJECTS*

MEASUREMENTS	SHOCK	RECOVERY
Body temperature (° C.)	37.8	37.3
Pulse rate	115	103
Arterial blood pressure (mm. Hg)	69/35	120/62
Auricular pressure (mm. H_2O)†	+5	+23
Cardiac index (liters per m^2b.s.)	1.96	2.99
Stroke volume (c.c. per beat)	28.3	39.0
Oxygen art.-ven. difference (c.c. per liter blood)	81	55
Plasma volume (c.c. per m^2b.s.)‡	1362	1629
Total blood volume (c.c. per m^2b.s.)‡	1665	2505
Ventilation (liters per m^2b.s.)	7.82	7.53
Oxygen intake (c.c. per m^2b.s.)	156.5	162.5
Art. blood CO_2 cont. at 40 mm. Hg (vol. %)†	35.8	43.5
pH_a (arterial blood)	7.31	7.37
Mixed venous blood O_2 sat. (%)	35.8	52.7

*4 with skeletal trauma, 2 with large hemorrhage.
†Average of 5.
‡Average of 4.

The average amount of blood transfused was 1170 c.c. and in addition an average amount of 1780 c.c. of saline solution was injected. The time interval between the two sets of measurements was, on an average, five hours (excepting one case in which the second study was forty-eight hours after the first). Improvement in circulation was striking; arterial blood pressure returned to normal levels while blood volume and cardiac output increased both approximately by 50 per cent of their previous

values; auricular pressure increased by 20 mm. H_2O, the three latter measurements being still below normal values. Alkali reserve and hydrogen-ion concentration showed similar trends. Hyperventilation and high pulse rate usually persisted. Oxygen consumption increased somewhat.

In brief, these data show the manner in which the circulation in peripheral failure, as seen in hemorrhagic or traumatic shock, can be restored by blood transfusion.

State of Renal Circulation in Relation to Shock

The material collected does not as yet permit an estimation of the effect of shock upon renal blood flow and rate of glomerular filtration. Data on one control group provided by head injuries, and isolated observations in other types of injuries with various states of the circulation, have been tabulated in Table VI. They should be viewed only as indicative of trends, to be supported by further investigation still in progress.

TABLE VI

RENAL CIRCULATION IN VARIOUS TYPES OF INJURIES

TYPE OF INJURY	PATIENT	MEAN ARTERIAL BLOOD PRESSURE	CARDIAC OUTPUT (L. PER MIN.)	GLOMERULAR FILTRATION (C.C. PER MIN.)	EFFECTIVE RENAL PLASMA FLOW (C.C. PER MIN.)	FILTRATION FRACTION	TOTAL RENAL BLOOD FLOW (C.C. PER MIN.)	RENAL FRACTION (%)	URINE FLOW (C.C. PER MIN.)
Normal control		--	--	130.0	688.0	.189	--	20.0	--
Head injury	Average of 5 cases	86	5.7	113.4	552.3	.205	990	17.3	4.62
Skeletal trauma—	J. V.	40	2.3	too low to be measured					
profound shock	A. A.*	54	5.1	2.6	22.7	.115	32	0.6	0.10
Hemorrhage									
(a) profound shock	H. M.	45	3.1	5.1	108.0	.047	160	4.5	0.34
(b) during recovery from shock	C. F.	90	3.1	42.9	194.9	.220	310	10.0	2.95
Abdominal injury									
(a) no shock	L. P.	72	7.2	110.1	690.0	.165	1352	18.8	5.60
(b) profound shock	J. D.	73	3.9	2.0	11.3	.178	22.0	0.6	0.17

*Very severe infusion reaction.

The average results in 5 cases of head injury, studied during periods of hypertension, show only slight deviation from normal findings, indicating that kidney circulation, like general circulation, remained essentially unaltered.

Results in 2 cases of severe shock due to skeletal trauma observed at their worst indicate extreme reduction in urine flow, too low to be measured accurately in J. V. In A. A., who suffered a severe infusion reaction with chills and fever throughout the renal study, the interpre-

tation is somewhat difficult; it is seen, however, that there was a very great decrease in filtration rate, effective plasma flow, or effective blood flow, and renal fraction.

In one hemorrhage patient in profound shock, the results are somewhat similar, with minor differences. In the second case of hemorrhage, given blood transfusion (blood bank) during the period of clearances, having a relatively high arterial mean pressure, the state of the renal circulation is somewhat better, especially the rate of filtration.

Of 2 cases of abdominal injury, one patient without shock showed normal renal circulatory dynamics. In the second case, a considerable reduction in effective renal blood flow was noted. This patient was in profound shock, in spite of the fact that the arterial blood pressure was not greatly decreased, the mean pressure being, as a matter of fact, the same as that of the first patient. A further interesting finding was a normal filtration fraction in this second (shock) case.

DISCUSSION

The descriptive data obtained in the present study indicate that traumatic shock is a rapid or precipitate failure of the circulation, usually associated with inadequate return flow of blood to the heart. This is in accord with the generally accepted view of shock, as developed in animal and in clinical studies.

If the above definition is valid, then the severity of shock should be consistently measured by the extent of decrease in cardiac output. Our results bear out this statement, the cardiac output being apparently a good index of shock in every case except two; one patient with fractured pelvis, who was having a violent shaking chill at the time of study, and one abdominal injury with fever and high oxygen consumption. The arteriovenous differences were, however, high in both these cases.

Equally consistent was the rise in cardiac output as the patient emerged from shock. This is shown in Table V. It will be better illustrated by individual case reports, in a subsequent paper.

The obvious question at this point is, how we have assigned the various patients into the categories of "shock" and "no shock," and whether we are not creating these categories simply on the basis of the measurements themselves. As stated in the body of the paper, the classification of each patient has been the best estimate that we have been able to make, using all available information—the clinical descriptions of the patient at the time, the sum of the measurements made, and especially the clinical course which the patient pursued. Using all these sources, there was actually but little if any doubt as to whether a given patient was in shock or not, at the time of initial study.

The anatomic factor immediately responsible for circulatory failure in our cases appeared in most instances to be a deficit in blood volume.

The average loss of blood volume, in cases in severe shock, was about 40 per cent. The equally important question whether a state of shock can develop without significant loss in circulating blood volume was not directly answered by the data presented in this paper. Further evidence on this problem, and its relation to so-called "primary" or "neurogenic" shock, will be offered in later papers.

Hemodilution, rather than hemoconcentration, was found in all cases of skeletal trauma with shock, and in all hemorrhage cases except one. While added plasma and saline solution might have been factors in this hemodilution, in the studies carried out during and after treatment, this could not apply to the initial measurements made usually soon after admission; and in these also, hemodilution was regularly demonstrated. In the skeletal trauma cases, the mechanism appeared to be chiefly extravascular blood loss (hemorrhage into tissues), followed by compensatory inflow of fluid from the tissues.

This finding (hemodilution) is of some importance in demonstrating that in these particular groups of cases of clinical shock, neither "increased capillary permeability" in the usually accepted sense, nor the consequent hemoconcentration, was present or played any part in the shock mechanism.

In burns and abdominal injuries, hemoconcentration was found.

If shock is due to failure of venous return, then the "effective pressure" of blood in the right auricle in states of shock should be consistently low. This we were not able to demonstrate precisely, since our auricular pressures were measured with reference to outside atmospheric pressure, rather than to intrathoracic pressure. This is an important point, since it is known that intrathoracic and intra-auricular pressures vary greatly with changes in form of respiration. Examples of this are, in fact, given in some of our patients with head injury, whose exaggerated stertorous breathing sucked the auricular pressures well below atmospheric levels, even though cardiac output was normal. It is also true that there is among normal subjects a considerable variation in the recorded right auricular pressures.

Admitting deviations due to irregular respiration and to individual differences, it is nonetheless probably significant, as shown in Tables III and IV, that the average figures for auricular pressure decreased progressively with increasing severity of shock, and (Table V) increased again as the patient recovered. Individual studies show instances of established shock in which auricular pressures were still within the lower limits of normal (+20 mm. of water); but we have had no case of shock with elevated auricular pressure, save for a patient with pulmonary embolus not included in this study. This is probably best considered as a special case, of acute failure of venous return to the left heart.

It can be stated, therefore, that our average figures on right auricular pressures suggest failure of venous return, in the patients in shock, and that none of the data are inconsistent with this hypothesis.

While the degree of shock was well correlated with the fall in arterial (femoral) blood pressure, this relationship was not constant in all instances. Two patients obviously in severe shock on admission had mean blood pressures within normal limits. Another had a rise of pressure to normal during the early part of treatment, without emerging from shock. These cases will be described in detail in the next paper of the series.

It is to be noted that the systolic pressure regularly fell more than the diastolic in shock, with, therefore, a reduced pulse pressure. During recovery, also, the systolic pressure increase was greater than that of the diastolic.

Low arterial pressure raises the question of inadequate coronary blood flow and of myocardial weakness. If this existed, it never extended to the point of congestive failure, since auricular pressures remained low. Thus, as already stated, the failure of venous return appeared to be the dominant factor.

Increase in pulse rate was variable and not a reliable criterion, or well correlated with the other data.

Adequate methods of determination of mean arterial pressure and of cardiac output have made possible the calculation of total peripheral vascular resistance. As will be seen from the figure and tables, the average values indicate that total peripheral resistance is not regularly increased in cases of shock. It should be emphasized, however, that the range of variation, from one individual case to another, was very large, extending from extremely low to moderately high values. Also, it was not infrequent to find low values for total peripheral resistance, when at the same time there was evidence of marked vasoconstriction in local vascular systems, specifically the skin of the extremities, and the kidneys. The cases of hemorrhage with shock showed, on the average, a somewhat higher peripheral resistance than the cases of skeletal trauma with shock, but this difference cannot be considered significant, with the present limited data.

That no consistent trend was observed may be due, among other causes, to great variations in the amount and rate of blood and fluid loss, changes in blood viscosity, and the degree of peripheral circulatory failure. Obviously, great differences existed in the pattern whereby the capacity of the vascular system as a whole adapted itself to loss in circulating blood volume. Detailed study of the adaptation in individual cases may give more useful information on this problem.

One local phase of vascular status receives some elucidation from the comparison of peripheral arm venous pressures with central auricular pressures. The tendency for this particular peripheral-central pressure

gradient to increase during shock gives support to the concept of narrowing of the venous channels in the extremities. It is not known whether this is on the basis of active venospasm or of passive collapse from lack of blood volume.

The considerable decrease in effective renal flow observed in the few subjects studied in a state of severe shock indicates either that the head pressure in the afferent artery is too low to promote filtration and effective flow and/or that active constriction is taking place. The latter mechanism would suggest that the kidneys, like the skin, are temporarily cut off from the circulation, thus making available more of the limited blood supply for immediately essential bodily functions. This adjustment of the renal circulation would play an important part in the attempt to maintain vascular hemostasis during periods of stress. The data on filtration fraction collected in patients in severe shock or during recovery from shock, suggest that the marked reduction in effective renal plasma flow is not primarily the result of failure of extraction of p-aminohippurate, but rather represents a true decrease in the circulation through the kidneys. These and other questions will be discussed in a separate paper dealing with the renal circulation in shock.

Total metabolism tended to be low in our cases of shock, acid-base levels decreased, with uncompensated acidosis. Blood lactic acid was much increased, accounting for a large part, if not all, of the fixed acid increase. Further data on this point will be presented in a subsequent paper. It might be noted that in two patients in profound shock, blood potassium was measured and found to be less than 6 mg. per 100 c.c. Uncompensated acidosis may not be present in the early hours following injury, even though the degree of shock is severe. Acidosis is, however, regularly present in later stages. It usually tends to disappear as recovery takes place, but in one patient (J. V.), the circulation recovered while acidosis actually became more marked.

It will have been apparent from this report that we conceive of shock as an end stage of circulatory failure which may be approached in many different ways. Each type of injury produces its own set of disabling factors, whose resultant and final effect is a form of failure of the circulation that we recognize as shock. In the limited clinical material reported in this study, the state of shock occurring in skeletal trauma was found to be closely similar to that in hemorrhage. Burn shock differed chiefly by the existence of massive loss of blood plasma; abdominal injuries also showed hemoconcentration.

Almost all of our patients in shock had considerable losses of blood volume and were of the "secondary" type. Vascular or vasomotor collapse (so-called primary or neurogenic factors) may well have been of essential importance also, in some cases; but it was not possible to identify these factors with certainty.

There are many important forms of injury that were not encountered in our material, as well as complicating factors such as exposure, dehydration, pre-existing emotional states of various kinds. Further cases which we have subsequently studied may partly fill in these gaps.

SUMMARY

1. Measurements of the circulation have been carried out in 36 clinical cases of injury of various types, with varying degrees of shock. The primary purpose has been a descriptive study of shock in man.

2. The basic measurements employed have included: (a) plasma and blood volumes; (b) arterial, and peripheral and central (right auricular) venous pressures; (c) cardiac output (direct Fick technique), (d) blood gases, hydrogen-ion concentration, lactic acid, proteins; (e) pulmonary ventilation and respiratory gas exchange; (f) renal clearances.

3. Critical evaluation of the methods used has been presented.

4. The clinical material consisted of 16 cases of severe skeletal trauma, 4 cases of hemorrhage, 4 cases of burn, 6 abdominal injuries, 6 cases of head injury.

5. The description derived from the data obtained conforms to the accepted view that traumatic shock in man is a rapid or precipitate failure of the circulation, usually associated with inadequate return flow of blood to the heart. The chief findings were decreased cardiac output, low pressure in right auricle, low arterial pressure, and decreased blood volume.

6. The cases of shock due to skeletal trauma and those due to hemorrhage, with one exception, all showed hemodilution rather than hemoconcentration. Burns and abdominal injuries showed hemoconcentration.

7. In 6 patients studied while in shock, or during recovery from shock, measurement of renal clearances showed marked reduction in effective renal blood flow, out of proportion to the decrease in the systemic blood flow, with a filtration fraction either normal or low.

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Review of Recent Meetings

REVIEW OF FIFTH ANNUAL MEETING OF THE SOCIETY OF UNIVERSITY SURGEONS

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THE Fifth Annual Meeting of the Society of University Surgeons was held in Chicago, Ill., at the University of Chicago Clinics, Feb. 11, 12, and 13, 1943. Papers presented are published in this issue of SURGERY.

In addition to those appearing here, **Edward L. Howes,** New York, discussed the rate and nature of epithelization of experimental wounds and described a photographic method for recording this phenomenon. **Herbert C. Maier,** New York, reviewed the physiologic disturbances caused by mediastinal displacement after pneumonectomy. **Frederick E. Kredel,** Charleston, S. C., presented further results and follow-up in a series of patients subjected to myopexy for amelioration of residual paralysis after cerebral thrombosis. **D. Slaughter,** Chicago, reviewed current conceptions of the indications for surgical and irradiation treatment of tumors of the skin. Repair of large bone defects by massive bone grafts was discussed by **D. B. Phemister,** Chicago. A series of patients with solitary fibrous lesions in the long bones was presented by **C. H. Hatcher,** Chicago. The various surgical procedures for relief of intractable pain were described by **E. A. Walker,** Chicago. **L. R. Dragstedt,** Chicago, discussed the physiologic principles in surgery of the pancreas. **C. B. Huggins,** Chicago, described experiments which demonstrated a fibrinolytic factor in prostatic fluid. This enzyme has previously been noted only as a product of bacterial metabolism but it would also seem to be a normal physiologic component of prostatic fluid. **H. P. Jenkins** and **Charles Dunham,** Chicago, presented their studies on the irritant properties of catgut tubing fluid and pointed out that "some of the irritant properties attributed in the past to the catgut itself are in reality due to residua of a high boiling point solvent used by the manufacturers in the preparation of catgut, such solvent not being completely removed before final tubing of the catgut." **S. M. Moore,** New York, discussed femoral hernia.*

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